Parental wellbeing and treatment adherence for children and adolescents with Phenylketonuria (PKU)

A thesis submitted to the The University of Manchester for the degree of Doctor of Clinical Psychology (ClinPsyD) in the Faculty of Biology, Medicine and Health

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Thesis Abstract

This thesis was submitted by Emma Medford as part of examination for the degree of Doctor of Clinical Psychology (ClinPsyD), in the Faculty of Biology, Medicine and Health at The University of Manchester. It was submitted in June 2016 for examination in September 2016. The title of the thesis is ‘Parental wellbeing and treatment adherence for children and adolescents with Phenylketonuria (PKU)’.

Phenylketonuria is a rare genetic disorder that causes cognitive impairment unless treated with a strict, protein-restricted diet. Due to the challenges of treatment adherence, caring for a child with PKU may affect parental wellbeing, and many children and adolescents have poor metabolic control. The overall aim of the thesis was to examine influences on parental wellbeing and treatment adherence.

Paper 1 is a systematic literature review of the demographic and psychosocial influences on blood phenylalanine concentration for children and adolescents with PKU. The aim was to identify factors that were robustly linked with metabolic control and could potentially be used to inform clinical practice. Findings from 29 identified studies indicated that whilst a number of demographic and psychosocial factors were related to metabolic control, the most reproducible association was with child age. Quality assessment of the studies indicated some methodological limitations, and a paucity of research in some areas highlighted the need for further research. The limitations of the evidence-base, clinical implications, and directions for future research are discussed.

Paper 2 presents an investigation of the psychological impact of parenting a child with PKU, the determinants of parental wellbeing, and the association between parental wellbeing and treatment adherence. Forty-six caregivers of children with PKU completed questionnaires examining psychological distress, parenting stress related to caring for a child with an illness, resilience, perceived social support, and child dependency. The proportion of blood phenylalanine concentrations within target range in the preceding year was used a measure of treatment adherence. Results showed that more than half of caregivers had clinical levels of psychological distress, which was predicted by their parenting stress and resilience. Whilst treatment adherence was not associated with parental distress, it was predicted by child age and caregiver perceived support from family. The limitations of the study, implications for clinical practice, and future research directions are discussed.

Paper 3 provides a critical evaluation of Papers 1 and 2 and a personal reflection of the research process.
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Acknowledgements

I would like to thank my academic supervisors, Anja Wittkowski and Dougal Hare, and field supervisors, Stewart Rust and Simon Jones, for their guidance throughout the research process. In addition, thank you to Philip Foden, statistician, for advice regarding statistical analyses, and to the National Society for PKU (NSPKU) for their support with the study.

I would also like to thank the caregivers who took part in the study, and the dietitians who assisted with recruitment. Last but not least, I would like to thank the 2013 cohort of ClinPsyD trainees for their friendship and support.
Demographic and psychosocial influences on treatment adherence for children and adolescents with PKU:

A systematic review

The following paper has been prepared for submission to the Journal of Inherited Metabolic Disease. Author guidelines can be found in Appendix A1. The word count has been extended for this version to add additional context.

Word count

Abstract: 217

Total excluding abstract, tables, figures and references: 4745

Number of figures and tables: 4
1.1 Abstract

Phenylketonuria (PKU) is a rare genetic disorder in which the amino acid phenylalanine cannot be sufficiently metabolised. Although a build-up of phenylalanine causes irreversible cognitive impairment, this can be prevented through a strict, lifelong, protein-restricted diet. Despite the severe consequences of poor metabolic control, many children and adolescents have phenylalanine levels above their recommended limits. This systematic review was the first to examine studies reporting demographic and/or psychosocial influences on blood phenylalanine levels, with the aim to identify factors that were robustly linked with metabolic control. Four electronic databases were searched, yielding 1808 articles. Articles were included if they reported a statistical examination of the association between one or more demographic or psychosocial factor(s) and metabolic control (as measured by blood phenylalanine concentration) for children and adolescents with PKU. Twenty-nine studies were selected for inclusion, which examined a range of child, parent and family factors related to blood phenylalanine levels. The most reproducible association was with child age, with metabolic control worsening with increasing age. This suggests that interventions promoting treatment adherence would be particularly beneficial for adolescents. There was a paucity of studies in some areas, and the quality of included studies varied; therefore, the conclusions of this review are preliminary. Research recommendations focus on promoting the growth of the evidence base to support clinical practice.

**Keywords:** Phenylketonuria, demographic, psychosocial, adherence, metabolic, children.

**Synopsis:** This systematic review identified that whilst a range of demographic and psychosocial variables were associated with metabolic control for children with phenylketonuria, the most reproducible association was with child age.
1.2 Introduction

Phenylketonuria (PKU, OMIM 261600) is a rare genetic disorder with an incidence of approximately 1 in 10,000 (NSPKU 2014). Due to a deficiency in the enzyme phenylalanine hydroxylase, the amino acid phenylalanine (phe) cannot be sufficiently metabolised. If left untreated, phe builds up in the body, causing severe and irreversible cognitive impairment; however, this can be prevented by a strict, lifelong, protein-restricted diet with amino acid supplements. Although the aim of dietary treatment is to maintain blood phe concentrations within an acceptable target range, which is monitored via frequent blood samples, currently there is no universally accepted range, with different countries, and different clinics within countries, using varied management guidelines (Ahring et al 2009; Feilliet et al 2010).

Poor metabolic control in children and adolescents is associated with increased cognitive difficulties and poorer academic achievement (e.g., Azen et al 1991; Chang et al 2000). A meta-analysis of 40 studies by Waisbren and colleagues (2007) showed a 1.3-3.1 point reduction in Intelligence Quotient (IQ) for each 100µmol/L increase in phe concentration. Furthermore, elevated phe levels have been associated with increased behavioural difficulties (Anjema et al 2011; Smith & Knowles 2000) and poorer psychological wellbeing (Brumm et al 2010; Clacy et al 2014). Whilst research indicates a biological basis of these difficulties due to raised phe levels (e.g., Christ et al 2009), the associations are likely to be bi-directional, with cognitive, mood, and behaviour difficulties having a negative impact on treatment adherence (e.g., Gentile et al 2009). Despite the severe consequences of poor dietary compliance, many children and adolescents have phe levels above the recommended range (Levy & Waisbren, 1994; MacDonald et al 2010; 2012; Walter et al 2002; Walter & White 2004). For example, in a study with 330 patients, a quarter of 0-9 year-olds, half of 10-14 year-olds, and more than three-quarters of 15-19 year-olds had phe levels above their maximum recommended limits (Walter et al 2002).
Very few studies have examined interventions to improve treatment adherence, and those that have are limited and mainly uncontrolled (e.g., MacDonald et al 2010). To inform interventions, it is necessary to identify the factors that affect treatment adherence for children and adolescents, and whether certain groups are at greater risk of poor metabolic control. A narrative review by MacDonald and colleagues (2010) highlighted a number of influences on dietary adherence, including patient age, social pressures, educational achievement of carers, and level of family cohesion. However, to date, there has been no systematic review of the factors affecting metabolic control for children and adolescents with PKU.

The aim of this review was to identify factors that were robustly linked with treatment adherence by examining studies reporting a statistical examination of the association between demographic and/or psychosocial factors relating to children and adolescents with PKU and their families, and metabolic control, as assessed by blood phe concentration.

1.3 Method
1.3.1 Search strategy
A systematic search of Ovid Medline, PsycInfo, Embase, and EBSCO CINAHL was performed on 11th December 2015. Search terms were Phenylketonuria AND adheren* OR diet* OR treatment OR complian* OR control OR phenylalanine OR outcome* OR concordan*. Search limitations included English language, children and adolescents (0-18 years), and years 1985-2015.

Figure 1 presents an outline of the search process based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al 2009). Studies were included if they 1) reported a statistical examination of the association between one or more demographic or psychosocial factor(s) and metabolic control (as measured by
blood phe concentration) for children and adolescents with PKU, 2) were in the English language, and 3) were published in a peer-reviewed journal between 1985-2015. Case series and review papers were excluded.

Figure 1. Flowchart demonstrating literature-review procedure

![Flowchart demonstrating literature-review procedure](image)

Titles and abstracts were screened for inclusion by the first author and relevant abstracts were selected for full-text review (n=62). Full text articles were assessed for eligibility and excluded if they did not meet the inclusion criteria. Any uncertainty about eligibility was resolved via discussion with another author. Six full text articles could not be accessed via...
inter-library loan, internet search, or by contacting authors via email. Twenty-eight papers were excluded: 16 did not examine the association between one or more demographic or psychosocial factor(s) and metabolic control and 12 reported a relationship but did not examine the association(s) statistically. Reference lists of included papers were manually examined, yielding one additional paper; thus, 29 studies were included. Data were extracted and entered into a database by the first author.

1.3.2 Quality assessment

The Quality Assessment Tool for Studies with Diverse Designs (QATSDD) was used to assess study quality (Sirriyeh et al. 2012). The QATSDD has shown good reliability and validity (Sirriyeh et al. 2012) and was chosen due to the diverse methodologies of the included studies.

The 14 QATSDD items relating to quantitative studies were rated on a 4-point scale from ‘not at all’ (0) to ‘complete’ (3). The item scores were summed to provide a total score, with a maximum score of 42. The first author rated all studies, and another author independently rated five studies (17%) to determine inter-rater reliability, which was good (k=.71).

1.4 Results

1.4.1 Characteristics of studies

Twenty-nine studies were included in this review, representing 1784 participants with PKU (including children, adolescents and adults, see Table 1 for participant age ranges). Sample sizes ranged from 13 to 167 participants and the sample characteristics that were reported varied greatly. Most studies provided information on patient age and sex, but few provided further details, such as socioeconomic status and ethnicity, alongside country of completion, with the most common country being the USA (n=11). Of the 29 studies, 19 were cross-
sectional, seven were longitudinal, and three were intervention studies. Two of the intervention studies were pre-post designs with no control group (Gleason et al 1992; Singh et al 2000), and one was a randomised controlled trial (Durham-Shearer et al 2008), with participants allocated to the intervention (educational resource) or control group (no educational resource). Whilst all studies statistically examined associations between demographic or psychosocial factors and blood phe levels, many studies (n=13) did not have this as their primary objective (see Table 1 for study aims).
<table>
<thead>
<tr>
<th>No</th>
<th>Study</th>
<th>Design</th>
<th>Primary aim</th>
<th>Age range (year)</th>
<th>Cohort characteristics</th>
<th>Child factors</th>
<th>Parent factors</th>
<th>Other family factors</th>
<th>Total quality score (out of 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Reber (1987)</td>
<td>Cross-sectional</td>
<td>Investigate family functioning and metabolic control.</td>
<td>&lt;8</td>
<td>N = 41; USA Mean family income = $25K. Mean maternal education = 12.9 years. Mean paternal education =13.1 years</td>
<td>N/A</td>
<td>-Education -Income -Distress -Marital satisfaction</td>
<td>-Family cohesion</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>Shulman (1991)</td>
<td>Cross-sectional</td>
<td>Investigate relationship of family variables to outcomes including metabolic control.</td>
<td>2-11</td>
<td>N = 43, 20 Male, 23 Female; USA Wide range of social background. Mean paternal education = 13.7 years Mean maternal education = 13.5 years.</td>
<td>N/A</td>
<td>-Education</td>
<td>-Family cohesion</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>Gleason (1992)</td>
<td>Intervention</td>
<td>Evaluate a treatment programme, including outcome of metabolic control.</td>
<td>12-19</td>
<td>N = 16, 9 Male, 7 Female</td>
<td>-Knowledge</td>
<td>N/A</td>
<td>N/A</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>McMurry (1992)</td>
<td>Cross-sectional</td>
<td>Evaluate the determinants of bone mineral status.</td>
<td>1-25</td>
<td>N = 26; USA</td>
<td>-Age</td>
<td>N/A</td>
<td>N/A</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>Verkerk (1994)</td>
<td>Cross-sectional</td>
<td>Analyse relationship between Phe levels and demographic factors.</td>
<td>&lt;1-5</td>
<td>N = 131; Netherlands</td>
<td>-Gender -Occupation -Country of origin</td>
<td>N/A</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Schulz (1995)</td>
<td>Cross-sectional</td>
<td>Assess food and nutrient intake and adherence to dietary therapy.</td>
<td>12-29</td>
<td>N = 99, 39 Male, 60 Female; Germany</td>
<td>-Age</td>
<td>N/A</td>
<td>N/A</td>
<td>19</td>
</tr>
<tr>
<td>No</td>
<td>Study</td>
<td>Design</td>
<td>Primary aim</td>
<td>Age range (year)</td>
<td>Cohort characteristics</td>
<td>Child factors</td>
<td>Parent factors</td>
<td>Other family factors</td>
<td>Total quality score (out of 42)</td>
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<tr>
<td>8</td>
<td>Al-Qadreh (1998)</td>
<td>Cross-sectional</td>
<td>Evaluate factors related to bone mineralisation.</td>
<td>2-17</td>
<td>N = 48, 20 Male, 28 Female; Greece</td>
<td>-Age</td>
<td>-Gender</td>
<td>N/A</td>
<td>26</td>
</tr>
<tr>
<td>9</td>
<td>Arnold (1998)</td>
<td>Cross-sectional</td>
<td>Investigate behavioural and motor problems.</td>
<td>1-8</td>
<td>N = 18, 8 Male, 10 Female; USA</td>
<td>-Age</td>
<td>N/A</td>
<td>N/A</td>
<td>28</td>
</tr>
<tr>
<td>10</td>
<td>Weglage (1999)</td>
<td>Longitudinal</td>
<td>Assess relationship between neuropsychological deficits and age and blood phe.</td>
<td>8-13</td>
<td>N = 20, 10 Male, 10 Female; Germany</td>
<td>-Age</td>
<td>N/A</td>
<td>N/A</td>
<td>25</td>
</tr>
<tr>
<td>11</td>
<td>Griffiths (2000)</td>
<td>Longitudinal</td>
<td>Examine relationship between cognitive skills and dietary control.</td>
<td>&lt;1-8</td>
<td>N = 57, 27 Male, 30 Female; UK Mean social class on a 7 point scale (defined in terms of chief earner income) = 4.56</td>
<td>-Age</td>
<td>-Income</td>
<td>N/A</td>
<td>28</td>
</tr>
<tr>
<td>12</td>
<td>Singh (2000)</td>
<td>Intervention</td>
<td>Evaluate a treatment programme, including outcome of metabolic control.</td>
<td>11-18</td>
<td>N = 13, 13 Female; USA 12 white, 1 of another descent.</td>
<td>-Knowledge</td>
<td>-Attitudes</td>
<td>N/A</td>
<td>28</td>
</tr>
<tr>
<td>14</td>
<td>Antshel (2004)</td>
<td>Cross-sectional</td>
<td>Examine attributions and association with treatment adherence.</td>
<td>8-16</td>
<td>N = 30; USA Predominantly lower-middle to middle class, with mean SES (Hollingshead, 1975) of 40.62. Approximately 87% caucasian, 4.7% africanamerican, 8.3% latino or Asian.</td>
<td>-Attributions</td>
<td>-Attributions</td>
<td>N/A</td>
<td>28</td>
</tr>
<tr>
<td>No</td>
<td>Study</td>
<td>Design</td>
<td>Primary aim</td>
<td>Age range (year)</td>
<td>Cohort characteristics</td>
<td>Child factors</td>
<td>Parent factors</td>
<td>Other family factors</td>
<td>Total quality score (out of 42)</td>
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<td>17</td>
<td>Olsson (2007)</td>
<td>Cross-sectional</td>
<td>Examine family factors relevant to dietary control.</td>
<td>8-19</td>
<td>N = 41; Sweden</td>
<td>- Age - Gender</td>
<td>- Education</td>
<td>- Marital status</td>
<td>27</td>
</tr>
<tr>
<td>18</td>
<td>VanZutphen (2007)</td>
<td>Cross-sectional</td>
<td>Examine relationships between executive functioning and adherence.</td>
<td>8-10</td>
<td>N = 15, 7 Male, 8 Female; USA</td>
<td>- Age</td>
<td>N/A</td>
<td>N/A</td>
<td>26</td>
</tr>
<tr>
<td>19</td>
<td>Durham-Shearer (2008)</td>
<td>Intervention</td>
<td>Evaluate a treatment programme, including outcome of metabolic control.</td>
<td>13-42</td>
<td>N = 32, 12 Male, 20 Female; UK</td>
<td>- Knowledge</td>
<td>N/A</td>
<td>N/A</td>
<td>31</td>
</tr>
<tr>
<td>20</td>
<td>Gokmen-Ozel (2008)</td>
<td>Cross-sectional</td>
<td>Determine how maternal knowledge was related to blood phe control.</td>
<td>1-15</td>
<td>N = 144, 81 Male, 63 Female; Turkey</td>
<td>- Age</td>
<td>- Knowledge</td>
<td>N/A</td>
<td>18</td>
</tr>
<tr>
<td>No</td>
<td>Study</td>
<td>Design</td>
<td>Primary aim</td>
<td>Age range (year)</td>
<td>Cohort characteristics</td>
<td>Child factors</td>
<td>Parent factors</td>
<td>Other family factors</td>
<td>Total quality score (out of 42)</td>
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</tr>
<tr>
<td>21</td>
<td>MacDonald (2008)</td>
<td>Cross-sectional</td>
<td>Compare maternal knowledge and education with effectiveness of blood phe control.</td>
<td>1-10</td>
<td>N = 46, 26 Male, 20 Female; UK 63% with annual income higher than national average. Paternal employment: full time 85%, unemployed 9%, NA 7%. Maternal employment: full time 9%, &gt;26 hours to &lt;full time 2%, &lt;26 hours per week 48%, not working 41%. 45 white caucasian, 1 pakiastani.</td>
<td>N/A</td>
<td>-Education -Employment status -Age -Income -Knowledge</td>
<td>-Family size</td>
<td>22</td>
</tr>
<tr>
<td>22</td>
<td>Vilaseca (2010)</td>
<td>Longitudinal</td>
<td>Assess relationship between dietary adherence and intelligence.</td>
<td>&lt;1-40</td>
<td>N = 105, 46 Male, 59 Female; Spain</td>
<td>-Age -Gender</td>
<td>N/A</td>
<td>N/A</td>
<td>25</td>
</tr>
<tr>
<td>23</td>
<td>Alaei (2011)</td>
<td>Cross-sectional</td>
<td>Assess relationships between dietary adherence and social status.</td>
<td>&lt;1-16</td>
<td>N = 105, 46 Male, 59 Female; Iran Maternal education: illiterate 4.8%, primary school 17.1%, high school 68.6%, higher education, 9.5%. Paternal education: illiterate 1%, primary school 18.1%, high school 65.7%, higher education 15.2%</td>
<td>N/A</td>
<td>-Education -Employment status</td>
<td>-Number of children with PKU -Marital status</td>
<td>18</td>
</tr>
<tr>
<td>24</td>
<td>Cotugno (2011)</td>
<td>Cross-sectional</td>
<td>Assess relationship between adherence and quality of life.</td>
<td>3-24</td>
<td>N = 41, 25 Male, 16 Female; Italy</td>
<td>-Age -Gender</td>
<td>N/A</td>
<td>N/A</td>
<td>21</td>
</tr>
<tr>
<td>25</td>
<td>MacDonald (2011)</td>
<td>Longitudinal</td>
<td>Determine the proportion with phe concentrations outside target guidelines.</td>
<td>1-56</td>
<td>N = 125, 52 Male, 73 Female; UK</td>
<td>-Gender</td>
<td>N/A</td>
<td>N/A</td>
<td>33</td>
</tr>
<tr>
<td>26</td>
<td>Viau (2011)</td>
<td>Longitudinal</td>
<td>Examine relationship between intelligence and phe levels.</td>
<td>6-18</td>
<td>N = 55, 27 Male, 28 Female; USA</td>
<td>-Age</td>
<td>N/A</td>
<td>N/A</td>
<td>34</td>
</tr>
<tr>
<td>27</td>
<td>Freehauf (2013)</td>
<td>Cross-sectional</td>
<td>Assess whether geographic proximity to clinic affected metabolic control.</td>
<td>&lt;1-21</td>
<td>N = 76, 43 Male, 33 Female; USA</td>
<td>-Age -Gender</td>
<td>N/A</td>
<td>-Distance to clinic</td>
<td>30</td>
</tr>
<tr>
<td>No</td>
<td>Study</td>
<td>Design</td>
<td>Primary aim</td>
<td>Age range (year)</td>
<td>Cohort characteristics</td>
<td>Child factors</td>
<td>Parent factors</td>
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<td>Total quality score (out of 42)</td>
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</tr>
<tr>
<td>28</td>
<td>Hartnett (2013)</td>
<td>Longitudinal</td>
<td>Assess how well patients were meeting therapeutic goals.</td>
<td>&lt;1-18</td>
<td>N = 33, 26 Male, 7 Female; Canada</td>
<td>-Age</td>
<td>N/A</td>
<td>N/A</td>
<td>28</td>
</tr>
<tr>
<td>29</td>
<td>Hood (2014)</td>
<td>Longitudinal</td>
<td>Examine relationships between blood phe and cognitive skills.</td>
<td>6-18</td>
<td>N = 47, 22 Male, 25 Female; USA</td>
<td>-Age</td>
<td>N/A</td>
<td>N/A</td>
<td>30</td>
</tr>
</tbody>
</table>
1.4.2 Quality ratings

Quality ratings ranged from 14 to 34 (% of maximum score range 33%-81%), with a mean of 26 (61%). Reasons for low ratings included having weak references to theory, limited rationale for choice of data collection tools, and minimal discussion of study limitations (see Table 2). Several studies also had small sample sizes, very few provided evidence that the sample size was considered in terms of analysis, and some did not provide a clear rationale for choice of analytic method. Furthermore, few studies considered statistical assessment of the reliability and validity of measurement tools, and only two studies provided evidence of user involvement in design. On observation, an association between study quality and year of publication or methodological design was not evident.

As this is the first review of the influence of psychosocial and demographic factors on metabolic control for children and adolescents, all studies were retained to provide a comprehensive overview of the available research.

1.4.3 Study findings

Studies were grouped according to whether they examined the influence of child, parent or other family factors on metabolic control: 24 assessed child factors, 14 parent factors, and eight reported on other family factors (Table 1). The main findings of each study are presented in Table 3.
Table 2. Overview of QATSDD item scores per study

<table>
<thead>
<tr>
<th>QATSDD item</th>
<th>Study number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Explicit theoretical framework</td>
<td>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29</td>
</tr>
<tr>
<td>2. Statement of aims/objectives in main body of report</td>
<td>3 3 3 2 2 1 1 3 3 3 2 3 2 3 3 2 3 1 2 2 1 3 3 3 3 2 3</td>
</tr>
<tr>
<td>3. Clear description of research setting</td>
<td>3 3 3 2 3 2 3 3 2 3 3 1 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3</td>
</tr>
<tr>
<td>4. Evidence of sample size considered in terms of analysis</td>
<td>0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 2 2 0 0 0</td>
</tr>
<tr>
<td>5. Representative sample of target group of a reasonable size</td>
<td>2 2 2 1 2 1 2 2 2 2 2 1 2 2 3 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2</td>
</tr>
<tr>
<td>6. Description of procedure for data collection</td>
<td>3 3 3 2 2 1 2 3 3 3 3 3 1 3 3 3 3 2 2 3 2 2 2 2 3 3 3 3 3 3 3 3 3 3</td>
</tr>
<tr>
<td>7. Rationale for choice of data collection tool(s)</td>
<td>3 1 3 1 2 1 1 2 2 3 2 3 1 2 2 2 2 2 2 2 1 1 2 1 1 3 3 3 2 2 3</td>
</tr>
<tr>
<td>8. Detailed recruitment data</td>
<td>2 0 3 0 2 0 1 1 1 0 1 1 0 3 3 3 3 2 2 0 1 1 2 0 1 1 2 2 1</td>
</tr>
<tr>
<td>9. Statistical assessment of reliability and validity of measurement tool(s)</td>
<td>1 2 2 0 2 0 1 1 1 1 1 2 0 1 1 2 0 1 0 0 0 1 1 0 1 2 1 1 1</td>
</tr>
<tr>
<td>10. Fit between stated research question and method of data collection</td>
<td>3 2 2 3 3 2 2 3 2 3 3 3 2 2 2 2 3 3 3 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3</td>
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<tr>
<td>11. Fit between research question and method of analysis</td>
<td>3 2 2 2 3 1 2 3 3 3 3 3 2 3 3 2 3 3 3 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3</td>
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<tr>
<td>12. Good justification for analytical method selected</td>
<td>2 2 2 2 3 0 1 2 3 1 3 3 1 2 1 1 3 2 2 2 2 3 1 1 3 3 3 2 3</td>
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<tr>
<td>13. Evidence of user involvement in design</td>
<td>0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 2 0 0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>14. Strengths and limitations critically discussed</td>
<td>3 2 1 2 1 2 2 1 3 1 2 0 0 2 2 3 2 1 2 1 2 1 0 0 3 3 3 3 3 3 2</td>
</tr>
<tr>
<td>Total score (out of 42)</td>
<td>31 24 28 20 29 14 19 26 28 25 28 28 15 28 28 29 27 26 31 18 22 25 18 21 33 34 30 28 30</td>
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<tr>
<td>Study</td>
<td>Cohort</td>
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<tr>
<td><strong>CHILD FACTORS</strong></td>
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<td>4</td>
<td>16</td>
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<td>5</td>
<td>26</td>
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<td>6</td>
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<td>Study</td>
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<td>Study</td>
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<td>29</td>
<td>47</td>
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<tr>
<td><strong>PARENT FACTORS</strong></td>
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<td>1</td>
<td>41</td>
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<tr>
<td>2</td>
<td>30</td>
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<td>Study</td>
<td>Cohort</td>
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<td>Study</td>
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<td>15</td>
<td>167</td>
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<td>16</td>
<td>19</td>
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</table>

-Blood phe was higher for children with parents who had emigrated from a different country and when parents answered that their relatives did not agree when their child deviated from the diet (subjective norm). -Blood phe was lower when parents experiences were that their child adhered well to the diet, even if their phe levels were sometimes too high (attitudes), and when parents answered that having their child eat the synthetic protein substitute was easy (self-efficacy). -Higher ratings of strategy effectiveness were associated with lower phe levels. -Higher ratings of problem frequency, problem difficulty, and problem affective intensity were associated with higher phe levels. -Parents who used authoritarian parenting strategies had children with higher phe levels than those who did not use these strategies.
<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Age range (year)</th>
<th>Measures /Tools</th>
<th>Target Phe level (µmol/L)</th>
<th>Analyses and statistics</th>
<th>Associated with blood phe</th>
<th>Not associated with blood phe</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>41</td>
<td>8-19</td>
<td>-Blood phe: mean phe across 3 periods: first year, 4th year, previous year. -Mean level of mother and father’s education collapsed into 3 levels: low, medium, high.</td>
<td>Childhood: &lt;500 Adolescence: &lt;600</td>
<td>Logistic regression to predict blood phe dichotomised into good and poor control. Educational level as a predictor: adjusted odds ratios = 2.56, 1.35 95% CIs 0.30/22.51, 0.1810.05, ps = 0.389, 0.770.</td>
<td>N/A</td>
<td>-Education</td>
<td>-Parent education did not predict phe levels dichotomised into good and poor control.</td>
</tr>
<tr>
<td>20</td>
<td>144</td>
<td>1-15</td>
<td>-Blood phe: median of previous 3 years. -Questionnaire examining knowledge of PKU.</td>
<td>120-360</td>
<td>Correlation between maternal exchange knowledge score and blood phe: r= -0.169, p = .043.</td>
<td>-Knowledge</td>
<td>N/A</td>
<td>-Higher exchange knowledge scores were associated with lower blood phe levels. However, no significant associations between total knowledge score, disease knowledge score, total dietary score and blood phe levels.</td>
</tr>
<tr>
<td>21</td>
<td>46</td>
<td>1-10</td>
<td>-Blood phe: Median lifetime phe &amp; median phe of previous year. -Education: qualification level. -Knowledge: Mother’s ability to calculate phe exchanges from food levels and estimate number of phe exchanges in food portions. Questionnaire examining knowledge of PKU.</td>
<td>120-360</td>
<td>Correlations between blood phe level and maternal knowledge, maternal phe exchange measuring ability, and demographic factors, ps &gt;.05.</td>
<td>N/A</td>
<td>-Age -Education -Employment status -Income -Knowledge</td>
<td>-Blood phe level was not significantly associated with parent age, educational level, employment status, income, or knowledge.</td>
</tr>
<tr>
<td>23</td>
<td>105</td>
<td>&lt;1-16</td>
<td>-Blood phe: mean phe of previous year. -Educational level: illiterate, primary school, high school, higher education. -Employment status: employed / unemployed</td>
<td>&lt;12 years: 120-360 &gt;12 years: 120-600</td>
<td>ANOVA: difference in blood phe for parents with different educational levels: p &gt; .05. -T-test: difference in blood phe for unemployed/employed parents: p = .03.</td>
<td>-Employment status</td>
<td>Education</td>
<td>-Blood phe levels did not differ significantly between children with parents of different educational levels. -Children with employed parents had significantly lower blood phe levels than unemployed.</td>
</tr>
<tr>
<td>Study</td>
<td>Cohort</td>
<td>Age range (year)</td>
<td>Measures /Tools</td>
<td>Target Phe level (µmol/L)</td>
<td>Analyses and statistics</td>
<td>Associated with blood phe</td>
<td>Not associated with blood phe</td>
<td>Main findings</td>
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<tr>
<td>1</td>
<td>41</td>
<td>&lt;8</td>
<td>-Blood phe: lifetime phe control - mean of 6 month medians. -Family cohesion: Family Adaptability and Cohesion Evaluation Scale - Version 2</td>
<td>&lt;600</td>
<td>Correlations between blood phe and family cohesion and adaptability: ps &gt;.05.</td>
<td>N/A</td>
<td>-Family Cohesion</td>
<td>-Family cohesion and adaptability were not significantly associated with blood phe levels.</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>1-16</td>
<td>-Blood phe: mean of previous 6 months. -Family cohesion: Family Environment Scale</td>
<td>120-600</td>
<td>Not reported</td>
<td>N/A</td>
<td>-Family cohesion</td>
<td>-Higher family cohesion was associated with lower blood phe levels.</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>2-11</td>
<td>-Blood phe: mean of previous year. -Family Cohesion: Family Adaptability and Cohesion Evaluation Scales</td>
<td>Not reported</td>
<td>-Correlation between blood phe and maternal rating of family cohesion: r = -.36, p &lt; .05, and paternal rating of family cohesion: r = -.34, p &lt; .05.</td>
<td>N/A</td>
<td>-Family cohesion</td>
<td>-The level of support and perceived cohesion within the family system and the degree of conflict between family members were not directly associated with phe levels outside of the normal range.</td>
</tr>
<tr>
<td>15</td>
<td>167</td>
<td>1-22</td>
<td>-Blood phe: mean of previous 3 years. previously 200-500, now lower during the first 12 years. -Marital status: married/cohabitant or separated/divorced.</td>
<td>Childhood: &lt;500 Adolescence: &lt;600</td>
<td>-Multiple regression to predict blood phe: No’ of children with PKU as a predictor: adjusted coefficients 0.57, 95% CI -12/-126, p = .102.</td>
<td>N/A</td>
<td>-Number of children with PKU</td>
<td>-After accounting for age and parent origin, having other children with PKU in the family did not predict blood phe levels.</td>
</tr>
<tr>
<td>17</td>
<td>41</td>
<td>8-19</td>
<td>-Blood phe: mean phe across 3 periods: first year, 4th year, previous year. - Marital status: married/cohabitant or separated/divorced.</td>
<td>Childhood: &lt;500 Adolescence: &lt;600</td>
<td>-Logistic regression analysis to predict blood phe dichotomised into good and poor control. Using marital status as a predictor: adjusted odds ratios: 7.46, CI 1.44-38.65, p = .017.</td>
<td>N/A</td>
<td>-Marital status</td>
<td>-Children with separated or divorced parents were more likely to have higher phe levels than children with married/cohabitant parents.</td>
</tr>
<tr>
<td>Study Cohort</td>
<td>Age range (year)</td>
<td>Measures /Tools</td>
<td>Target Phe level (µmol/L)</td>
<td>Analyses and statistics</td>
<td>Associated with blood phe</td>
<td>Not associated with blood phe</td>
<td>Main findings</td>
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<tr>
<td>21</td>
<td>46</td>
<td>1-10</td>
<td>Blood phe: median lifetime phe and median phe of previous year.</td>
<td>120-360.</td>
<td>Correlation between family size and blood phe: p&gt;.05.</td>
<td>N/A</td>
<td>-Family size was not significantly associated with blood phe levels.</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>105</td>
<td>&lt;1-16</td>
<td>Blood phe: mean of previous year. Marital status: divorced /non-divorced</td>
<td>&lt;12 years: 120-360 &gt;12 years: 120-600</td>
<td>-Correlation between blood phe and number of children in the family: r = 0.1, p = .08, and number of children with PKU: r = 0.43, p &lt; .001. -Mann Whitney U test: Significant increase in mean phe rank for patients whose parents were divorced: p = 0.02.</td>
<td>-Number of children with PKU -Marital status</td>
<td>-Family size was not significantly associated with the number of children in the family. -Higher blood phe was associated with increased number of children with PKU in the family. -Children with divorced parents had higher blood phe levels than children with non-divorced parents.</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>76</td>
<td>&lt;1-21</td>
<td>Blood phe: mean and median phe over 5 year period. Difference scores between median phe and target phe. Distance to clinic: grouped into &lt;35 miles away /&lt;100 miles away /&gt;100 miles away</td>
<td>&lt;12 years: &lt;360 &gt;12 years: &lt;600</td>
<td>-Correlation between blood phe as compared to target and distance to clinic: p = 0.62. -Difference in blood phe for different distances to clinic: p = 0.3. -Chi square test: difference in the proportion of patients with blood phe above target for patients living different distances to clinic: p = 0.41.</td>
<td>N/A</td>
<td>-Distance to clinic</td>
<td></td>
</tr>
</tbody>
</table>

1.4.4 Child Factors

1.4.4.1 Age

Sixteen studies examined the association between child age and metabolic control. Seven studies used correlational analyses: six reported a positive correlation (Al-Qadreh et al 1998; Freehauf et al 2013; McMurry et al 1992; Schulz & Bremer 1995; VanZutphen et al 2007; Vilaseca et al 2010), and one reported no significant correlation (Arnold et al 1998). Five Pearson’s r coefficients ranged from 0.35-0.64, and one Spearman’s rho coefficient was 0.62 (Freehauf et al 2013). However, the positive correlation reported by Vilaseca and colleagues (2010; Pearson’s r=0.63) might be partially explained by an increase in target blood phe level for 6-12 year-olds (<600 µmol/L) compared to under 6-year-olds (<480 µmol/L). An additional study (Crone et al 2005) found a quadratic rather than linear association between age and metabolic control, with blood phe increasing after 13 years.

One study (Freehauf et al 2013) found a positive correlation between age and blood phe for over 12-year-olds (Spearman’s rho=0.48), but not for under 12-year-olds. When using a measure of difference score between phe level and target level, a significant correlation remained with age for over 12-year-olds (Spearman’s rho=0.48), indicating a progressive reduction of metabolic control from adolescence. If this is the case, this could explain the lack of a significant correlation found in Arnold et al’s (1998) study, which examined the association between age and blood phe in 1-8-year-olds. Nevertheless, in a sample of 8-19-year-olds, age was not significantly associated with metabolic control when phe was dichotomised into poor and good control (Olsson et al 2007). However, as only a small proportion had poor control (n=14), there might not have been sufficient statistical power to identify an association.

Two studies (Griffiths et al 2000; Viau et al 2011) found that blood phe levels significantly increased year-by-year with age, and eight studies found that blood phe was
significantly higher for those above six years of age (Gokmen-Ozel et al 2008; Vilaseca et al 2010), eight years (Al-Qadreh et al 1998), 10 years (Hood et al 2014), 12 years (McMurry et al 1992; Vilaseca et al 2010), and 14 years (Weglage et al 1999). However, in Gokmen-Ozel and colleagues’ (2008) study, the increase in phe for over 6-year-olds compared to under 6-year-olds might be partially explained by an increase in target phe levels from age six.

Two studies examined the proportion of children who achieved good metabolic control and found contrasting results: Vilaseca and colleagues (2010) discovered that the proportion with good control decreased with increasing age (from under 6 years, to 6-12 years, to over 12 years), but Hartnett et al (2013) found no significant difference between under 6 and 6-12-year-olds. Furthermore, Cotugno and colleagues (2011) observed that more over 10-year-olds achieved target phe levels than under 10-year-olds, contradicting studies showing reduced metabolic control with age. These findings might reflect a higher likelihood of reduced metabolic control from adolescence rather than from younger ages.

Three studies (Hartnett et al 2013; Hood et al 2014; Viau et al 2011) examined the relationship between age and variability in phe levels, but their findings showed no significant associations.

1.4.4.2 Gender

Seven studies examined the association between gender of the child and metabolic control. Six studies found no significant relationship: blood phe levels (Al-Qadreh et al 1998; Freehauf et al 2013; Vilaseca et al 2010) and the proportion achieving target levels (Cotugno et al 2011) did not significantly differ between male and female children, and gender did not predict phe levels (Olsson et al 2007; Verkerk et al 1994). However, Olsson and colleagues (2007) noted that gender had a borderline statistical significance in a subgroup of children whose parents had not separated, with a tendency toward lower phe levels in
female children. In addition, in a sample of 6-17-year olds, the proportion with 70% or more of their phe levels within target range was significantly higher for females than males (MacDonald et al 2011).

1.4.4.3 Child knowledge

Four studies examined the association between child knowledge of PKU and metabolic control, with each study using a different knowledge questionnaire developed in line with previous research. Three studies evaluated the impact of adolescent treatment programmes designed to improve treatment adherence (Durham-Shearer et al 2008; Gleason et al 1992; Singh et al 2000). Gleason and colleagues (1992) identified that post-intervention improvements in knowledge were accompanied by reductions in blood phe level; however, other treatment factors, including motivational techniques, might have led to reduced levels rather than improved knowledge. Two studies (Durham-Shearer et al 2008; Singh et al 2000) reported that post-intervention improvements in PKU knowledge were not accompanied by sustained reductions in blood phe. However, the intervention studies were limited by small sample sizes (n ranged from 16-32), and did not examine the direct association between PKU knowledge and metabolic control. An additional study (Bekhof et al 2003) found that knowledge of PKU did not significantly predict blood phe levels.

1.4.4.4 Other child factors

In their examination of the association between metabolic control and child attributional style, Antshel and colleagues (2004) measured attributions using locus of control ratings for vignettes describing a young person with behavioural dysregulation or academic difficulties. Locus of control ratings were significantly correlated with blood phe level (Pearson’s r=.61 for behavioural dysregulation vignettes and .43 for academic difficulties vignettes), with higher blood phe associated with a higher external locus of control. They
suggested that children with a higher internal locus of control assumed more personal responsibility for treatment adherence, resulting in better metabolic control, or that children with a higher external locus of control felt more powerless over their condition, leading to reduced treatment adherence.

In their intervention study examining the associations between metabolic control, attitudes, and health beliefs relating to PKU, Singh et al (2000) found that post-intervention improvements in attitudes and health beliefs (assessed by questionnaires based on previous research) were not accompanied by sustained reductions in blood phe levels. Finally, Ievers-Landis et al (2005) examined the associations between adherence strategies, perceived strategy effectiveness, perceived problem frequency and difficulty (assessed by semi-structured interview and Likert scales), and metabolic control. Higher child perceived strategy effectiveness was associated with lower blood phe levels (Pearson’s r = -0.68), but perceived problem frequency and difficulty were not significantly associated. In addition, children who used strategies coded as maladaptive for treatment adherence (e.g., avoiding problems) had higher blood phe levels than those who did not use maladaptive strategies.

1.4.5 Parent factors

1.4.5.1 Income

Three studies examined the association between parent income and metabolic control. Whilst Griffiths and colleagues (2000) found that chief earner income was positively correlated with blood phe (Pearson’s r = 0.28), two other studies (MacDonald et al 2008; Reber et al 1987) failed to identify a significant correlation between metabolic control and income. This inconsistency could be due to the different measures used, as Griffiths and colleagues (2000) used income of the chief earner rather than overall household income.
1.4.5.2 Employment/Occupational status

Of the three studies examining the association between parent employment or occupational status and metabolic control, only Alaei et al (2011) noted that children with employed parents had significantly lower blood phe levels than children with unemployed parents. Employment status was not significantly associated with metabolic control in MacDonald et al’s (2008) study and occupational level did not predict blood phe in Verkerk and colleagues’ (1994) study.

1.4.5.3 Education

Five studies examined the association between parents’ educational level and metabolic control. According to Reber et al (1987) and MacDonald and colleagues (2008), blood phe was not significantly associated with parents’ level of education. Alaei and colleagues (2011) found that metabolic control was not significantly different for parents with different educational levels. Although Olsson et al (2007) noted that parental educational level did not predict phe levels dichotomised into good and poor control, Shulman and colleagues (1991) identified that children’s concurrent phe level was correlated with maternal (Pearson’s r= - .27) and paternal education (r=-.28), with higher education associated with lower blood phe. This inconsistency could be due to different study characteristics such as country and year.

1.4.5.4 Parent knowledge

Three studies examined the association between parent knowledge of PKU (using questionnaires based on previous research) and metabolic control. Whilst Gokmen-Ozel et al (2008) found a significant negative correlation between maternal exchange knowledge score and blood phe level (Pearson’s r= -.17), total knowledge scores were not significantly associated with metabolic control. Similarly, MacDonald and colleagues (2008) reported
that mother’s total knowledge of PKU was not associated with phe level, nor was their ability to calculate exchanges or estimate the number of phe exchanges in food portions. Although Bekhof et al (2003) noted that higher parent knowledge predicted lower blood phe levels, this association disappeared when other confounders were adjusted for (pre-treatment phe, dietary phe tolerance, parent age, parent educational level, and ethnicity).

1.4.5.5 Skills, strategies and psychological factors

Fehrenbach and Peterson (1989) examined the associations between parent problem-solving skills, parenting strategies, and metabolic control. Children with good metabolic control had parents who produced a higher number and higher quality of verbal responses to PKU problem scenarios than children with poor metabolic control. Furthermore, those with good metabolic control had families that were organised in a more hierarchical manner with more firmly fixed rules. However, Ievers-Landis et al (2005) observed that parents using strategies coded as authoritarian had children with higher phe levels than those who did not. In addition, higher parent perceived strategy effectiveness was associated with lower phe levels (Pearson’s $r=-.64$), and higher ratings of problem frequency ($r=.55$), problem difficulty ($r=.79$) and affective intensity ($r=.61$) were associated with higher phe levels.

Crone and colleagues (2005) examined the associations between parent attitudes, subjective norms, self-efficacy and metabolic control. Children’s blood phe levels were lower when parents’ experiences were that their child adhered well to the diet, even if their phe levels were sometimes too high (attitudes), and when parents answered that having their child eat the synthetic protein substitute was easy (self-efficacy). However, blood phe levels were higher when parents answered that their relatives did not agree when their child deviated from the diet (subjective norm).

Antshel and colleagues (2004) examined the association between metabolic control and parent attributional style, measured using locus of control ratings for vignettes
describing a young person with behavioural dysregulation or academic difficulties. Locus of control ratings were significantly correlated with blood phe level (Pearson’s r=.69 for behavioural dysregulation vignettes and .52 for academic difficulties vignettes), with higher blood phe associated with a higher external locus of control. The authors suggested that parents with a higher external locus of control felt more powerless in relation to their child’s condition, leading to reduced efforts in supporting treatment adherence.

Finally, two studies examined the relationship between parental distress and metabolic control, and found that parental distress, parenting-related stress, and marital satisfaction were not significantly associated with phe levels (Reber et al 1987), and level of external stress was not significantly different for those with good and poor control (Fehrenbach & Peterson 1989).

1.4.5.6 Other demographic factors

Two studies from the Netherlands examined the association between parental country of origin and metabolic control (Crone et al 2005; Verkerk et al 1994). Children with parents who had emigrated from a different country had higher blood phe levels than children with Dutch parents, possibly because of barriers to accessing health care services for some immigrants, such as language difficulties. In their study of the relationship between parent age and metabolic control, MacDonald et al (2008) found no significant association.

1.4.6 Other family factors

1.4.6.1 Family composition

Four studies examined the associations between family composition factors and metabolic control. Children with separated or divorced parents were more likely to have higher phe levels than children with married or cohabitant parents (Alaei et al 2011; Olsson et al 2007), but family size/number of children was not associated with metabolic control (Alaei et al
2011; MacDonald et al 2008). Whilst Alaei et al (2011) found that blood phe was positively correlated with the number of children with PKU (strength of correlation not reported), Crone and colleagues (2005) noted that the number of children with PKU did not predict phe level.

1.4.6.2 Family cohesion

Three studies published in the late 1980s/early 1990s examined the association between family cohesion and metabolic control using parent questionnaires. Two studies used the Family Adaptability and Cohesion Evaluation Scale (Reber et al 1987; Shulman et al 1991) and one used the Family Environment Scale (Fehrenbach & Peterson 1989). Although Shulman and colleagues (1991) reported that lower blood phe level was moderately associated with higher paternal and maternal family cohesion scores (Pearson’s r=-.34; .36, respectively), Reber et al (1987) and Fehrenbach and Peterson (1989) found no significant association with metabolic control.

1.4.6.3 Distance to clinic

A study by Freehauf et al (2013) found no significant association between distance from home to clinic and metabolic control.

1.5 Discussion

This systematic review examined 29 identified studies reporting a statistical examination of the association between one or more demographic or psychosocial factor(s) and metabolic control (as measured by blood phe concentration) for children and adolescents with PKU. Only studies reporting statistical analyses were included in order to identify the factors most robustly linked with metabolic control. In summary, the included studies examined a range of child, parent and family factors and indicated some strong associations with blood phe
levels. However, there were some areas of investigation with a paucity of studies, highlighting a need for further research in this area.

This review suggests that the most reproducible factor associated with blood phe level currently is child age. Sixteen studies examined child age, with the majority finding a progressive reduction in metabolic control with age, and some suggesting that this occurred from adolescence. Reported correlations between age and metabolic control ranged from 0.35-0.64, indicating moderate to large associations. A similar influence of age has been found in children with diabetes (Neylon et al 2013), implying that this association may be common in other metabolic disorders. With increasing age, it is likely that increased independency from the family and heightened social pressures, for example, around food and lifestyle, contribute to reduced dietary adherence (Levy & Waisbren, 1994). Interestingly, all 16 studies reporting an association with age did not examine this as their primary aim, suggesting that demographic data are frequently examined in health-related studies as a secondary objective.

Following age, the next most reproducible factor was child gender, with six studies indicating no association with gender and one study finding that more females had 70% or more of their phe levels within target range than males (MacDonald et al 2011). In this study, the endpoint measure of 70% or more levels within target range might have allowed greater sensitivity with regards to identifying more subtle differences in metabolic control between males and females.

Due to the small numbers of studies examining other child, parent, and family factors, it is difficult to draw firm conclusions regarding their influence. However, regarding child factors, the available research indicated that blood phe level was not associated with child knowledge of PKU, attitudes, health beliefs, perceived problem frequency, or perceived problem difficulty. Conversely, blood phe level showed moderate to large correlations with child attributional style, a strong correlation with perceived strategy
effectiveness, and was significantly different for those using maladaptive and non-maladaptive strategies.

Regarding parent and family factors, the available findings indicated that metabolic control was associated with parenting strategies, attitudes, subjective norms, self-efficacy, perceived strategy effectiveness, perceived problem frequency, perceived problem difficulty, attributional style, affective intensity of problems, country of origin, and marital status. It is possible that some of these associations were bi-directional; for example, higher parental self-efficacy may have fostered better treatment adherence, which may have led to increased self-efficacy with regards to managing the diet.

Metabolic control was not associated with or inconsistently associated with parent knowledge of PKU, parent age, parent distress, family size, number of children with PKU in the family, family cohesion, geographic proximity to clinic, and socioeconomic factors, such as parent income, education, and occupation. The inconsistencies in findings between studies could be a result of different study methodologies, measures and cohort characteristics. For example, in relation to socioeconomic factors, participants from different countries may experience different levels of social inequality, and therefore factors such as unemployment may have a greater impact on treatment adherence and availability of low protein foods and food substitutes in some countries than others.

1.5.1 Limitations

Whilst this review identified a number of factors related to metabolic control, it was difficult to draw firm conclusions due to both a paucity of studies in some areas of investigation and some inconsistent findings. Furthermore, the strength of conclusions that can be drawn is limited by the varied quality of the included studies. As highlighted by the QATSDD ratings, a number of studies had small sample sizes with no evidence of consideration of the sample size in terms of analysis, meaning that the power of some studies could have been
limited. However, it should be noted that the potential recruitment pool of young people with PKU is small due to the rarity of the condition, and hence small sample sizes are common. Nevertheless, as studies often provided scarce sample descriptions and the majority used cross-sectional methodology, it is difficult to draw conclusions about cause and effect influences on metabolic control. Finally, as there was limited availability of articles during the search process (six full-text articles were not available), it is unknown whether these would have met the inclusion criteria and contributed to the results and conclusions of this review.

1.5.2 Recommendations for clinical practice

This review indicates that certain groups of young people may be at higher risk of poor treatment adherence, particularly older children and adolescents. It is therefore important that clinicians and parents are aware of the tendency for worsening metabolic control with age and consider providing extra support to older children (around age 12 and above). Whilst PKU clinics routinely provide information about PKU and associated dietary treatment to young people and their carers, this review indicated that child knowledge of PKU was not associated with metabolic control, and parental knowledge was only weakly or inconsistently associated. This suggests that treatment knowledge is necessary but not sufficient for dietary adherence, and therefore interventions to promote treatment adherence should incorporate additional factors. In the UK, PKU management guidelines (NSPKU 2014) recommend that services for young people with PKU consist of multidisciplinary teams, with a clinical psychologist to focus on, among other things, promoting ‘patient and parent motivation to comply with treatment’. Although this review cannot draw firm conclusions, the findings suggest that psychological constructs including child and parent attributional style, attitudes and self-efficacy could be targets for intervention.
Due to the wide range of potential influences on metabolic control, as highlighted in this review, it is important that idiosyncratic psychological formulations and interventions take into account a range of possible contributing factors. However, as there is currently limited research investigating many psychosocial influences, it may be useful for clinicians to also draw on the literature examining predictors of treatment adherence in other metabolic conditions (e.g., Neylon et al 2013).

1.5.3 Recommendations for future research

This review highlights that there is a paucity of studies examining many demographic or psychosocial influences on metabolic control for young people with PKU, and therefore further research is needed. For example, regarding literature on other metabolic conditions, such as diabetes, metabolic control has been associated with factors such as ethnicity, personality characteristics and coping style (Neylon et al 2013). Whilst currently unexplored, it is possible that these factors also influence treatment adherence for children with PKU. One of the reasons for limited research in this field is the small sampling pool due to the rarity of the condition, which makes it difficult to recruit sufficient numbers of patients. It is therefore recommended that future studies promote increased recruitment by working more in partnership with clinicians, patients, carers and support groups (DeWard et al 2014).

It is important that future studies provide more information about participant characteristics, such as socioeconomic details, particularly as these may impact treatment adherence outcomes. In addition, more longitudinal studies are needed to help ascertain cause and effect influences on metabolic control and to explore whether other variables mediate the associations between factors such as age and metabolic control, such as increased social pressures. Although this is currently an emerging evidence-base, further
studies could design and examine interventions to improve treatment adherence, informed by the factors highlighted in this review.

1.5.4 Conclusion

This review was the first to systematically examine studies reporting a statistical examination of the association between demographic or psychosocial factors and metabolic control for children and adolescents with PKU. Findings suggested that the most reproducible association was with child age, with control worsening with increasing age. Whilst a number of other factors were associated with blood phe levels, the evidence-base was small with some methodological limitations, and therefore the conclusions of this review are preliminary. This review highlights a paucity of research examining many demographic or psychosocial influences on metabolic control for young people with PKU. Research recommendations are therefore targeted towards promoting the growth of the evidence-base to support clinical practice.
1.6 References


NSPKU (National Society for PKU; 2014) Management of Phenylketonuria: A consensus


of mean phenylalanine levels during the first five years of life in patients with phenylketonuria who were treated early. *Acta Paediatrica Supplement* 83: 70-2


Psychological wellbeing and treatment adherence for parents of children with Phenylketonuria (PKU)

The following paper has been prepared for submission to the *Journal of Inherited Metabolic Disease*. Author guidelines can be found in Appendix A1. The word count has been extended for this version to add additional context.

**Word count**

Abstract: 231

Total excluding abstract, tables, figures and references: 4110

Number of figures and tables: 4
2.1 Abstract
Phenylketonuria (PKU) is a rare metabolic disorder that causes cognitive impairment unless treated with a strict, protein-restricted diet. Due to the challenges of treatment adherence, caring for a child with PKU may affect parental wellbeing. As few studies have examined influences on parental wellbeing and its association with treatment adherence, this was the objective of the current study. Forty-six primary caregivers of children with PKU completed questionnaires examining psychological distress, parenting stress related to caring for a child with an illness, resilience, perceived social support, and child dependency. Treatment adherence was assessed using the proportion of blood phenylalanine concentrations within target range in the preceding year. Results showed that 59% of caregivers had clinical levels of psychological distress, which was predicted by their parenting stress and resilience. Whilst the proportion of blood phenylalanine concentrations in range was not associated with parental distress, it was predicted by child age and caregiver perceived support from family. The results indicated that despite experiencing high levels of distress, caregivers’ ability to adhere to treatment was not affected. Interventions to reduce parenting stress and boost caregiver resilience may have a positive effect on parental wellbeing. Additionally, interventions to promote treatment adherence may be of particular benefit for parents of older children, with a focus on promoting support from family members. Further research with larger sample sizes and longitudinal designs is needed to further establish causal mechanisms.

**Keywords:** Phenylketonuria, parent, wellbeing, distress, adherence, children.

**Synopsis:** This study identified that for parents of children with phenylketonuria, parental psychological wellbeing was predicted by parenting stress and resilience, whereas treatment adherence was predicted by child age and perceived support from family.
2.2 Introduction

Phenylketonuria (PKU, OMIM 261600) is a rare genetic disorder in which the amino acid phenylalanine (phe) cannot be sufficiently metabolised. Although an accumulation of phe causes severe and irreversible cognitive impairment, this can be prevented through dietary intervention. The main treatment is a strict, lifelong, protein-restricted diet with amino acid supplements. Parents are required to closely supervise the nutritional intake of their child and submit frequent blood samples to monitor blood phe concentrations against an acceptable target range (NSPKU 2014).

Given the effort required for treatment adherence and the severe consequences of poor compliance, caring for a child with PKU brings additional challenges to the parenting role. Indeed, a qualitative study with parents of children with PKU revealed that handling the diet was the largest problem they faced (Awiszus & Unger 1990). These additional challenges have a possible detrimental impact on parental wellbeing, with studies showing higher levels of depression and anxiety in mothers of children with PKU than mothers of healthy children (Gundaz et al 2015), and mild to severe levels of depression, anxiety and stress in over half of parents of children with PKU (Mahmoudi-Gharaei et al 2011). However, findings are mixed, with other studies reporting comparable levels of psychological distress and Health Related Quality of Life (HRQoL) compared to parents of healthy children (Kazak et al 1988; Ten Hoedt et al 2011), and high Parental Quality of Life (PQoL) for three quarters of parents (Fidika et al 2013).

To adequately support parents of children with PKU, it is important to understand the determinants of their psychological wellbeing. Fidika et al (2013) found that PQoL was predicted by family stress and perceived social support, whereas Ten Hoedt et al (2011) observed that HRQoL was affected by emotional support and loss of friendship. Both studies reported that parental QoL was lower for parents with younger children, possibly due to greater parental responsibility for dietary adherence when the child was young.
(Fidika et al 2013). Conversely, parental anxiety and depression scores were not associated with child age in a study by Gundaz and colleagues (2015).

Very few studies have examined the relationship between parental psychological wellbeing and treatment adherence. A study by Reber et al (1987), with 30 parents, found no significant difference between parents of children with good and poor metabolic control on a measure of external life stress. Similarly, Fehrenbach and Peterson (1989), in a study with 41 parents, observed that parental levels of anxiety and depression were not significantly associated with metabolic control. However, these studies were conducted nearly thirty years ago, and more recent research with other metabolic conditions has indicated an association between parental wellbeing and treatment adherence. For example, MacKey et al (2014) noted that for children with diabetes, increased maternal depressive symptoms were associated with less parental monitoring, which was in turn associated with poorer adherence and metabolic control. It is therefore possible that psychological wellbeing also impacts treatment adherence for parents of children with PKU.

The objectives of this study were to (1) examine the psychological impact of parenting a child with PKU, (2) examine influences on parental psychological wellbeing, and (3) examine the relationship between parental wellbeing and treatment adherence. It was expected that parents would have high levels of psychological distress, and that this would be predicted by their parenting stress related to caring for a child with an illness, resilience, perceived social support, and level of child dependency. In addition, it was hypothesised that treatment adherence would be associated with parental psychological distress and other parent factors (resilience, perceived social support, and child dependency).
2.3 Method

2.3.1 Participants

Primary caregivers of children with PKU attending three metabolic clinics in the North West of the UK (Manchester, Liverpool, and Bradford) were invited to participate. Caregivers were eligible to take part if their child was between 0-16 years old and had been diagnosed with PKU at newborn screening. Caregivers were excluded if they could not read, write and speak English, or if there were any other significant health problems or caring responsibilities that could impact their psychological wellbeing, as determined by the clinical team. Written consent was obtained from caregivers.

2.3.2 Measures

2.3.2.1 Demographics

A demographics questionnaire was used to obtain caregiver date of birth, gender, language, relationship to child, highest qualification, and average family income (see Appendix B1).

2.3.2.2 Psychological distress

The General Health Questionnaire-12 (GHQ-12; Goldberg & Williams 1988) was used to assess caregiver psychological distress. It is a brief self-report measure, with higher scores indicating higher levels of distress (anxiety and depression), and scores over 12 indicating distress within the clinical range (Goldberg et al 1997). The GHQ-12 has good psychometric properties (e.g., Goldberg & Williams 1988) and showed a high level of internal consistency in the current study: $\alpha=.87$.

2.3.2.3 Parenting stress

Given the possible illness-specific stressors for parents, such as negotiating medical care and communication with the healthcare team, the Pediatric Inventory for Parents (PIP;
Streisand et al. (2001) was used to measure caregiver stress related to caring for a child with an illness. The PIP is a self-report measure with four sub-scales: communication, medical care, emotional distress and role function, which combine to create a total difficulty and a total frequency score. These total scores were used in this study, and had high levels of internal consistency: $\alpha = .94$ and $.95$, respectively.

### 2.3.2.4 Resilience

Caregiver resilience was assessed using the Resilience Scale for Adults (RSA; Friborg et al. 2006), a self-report measure with six sub-scales: perception of self, planned future, social competency, structured style, family cohesion and social resources, which combine to create a total score. Higher scores indicate higher levels of protective resilience factors. Compared to other resilience measures, the RSA has shown high psychometric ratings (Windle et al. 2011). The total score was used in this study, and internal consistency was high: $\alpha = .88$.

### 2.3.2.5 Social support

Perceived social support was assessed using the Multidimensional Scale of Perceived Social Support (MSPSS; Zimet et al. 1988), a self-report measure with three sub-scales: family, friends, and significant other, which combine to create a total score. The MSPSS has strong psychometric properties (e.g., Zimet et al. 1990), and had good internal consistency in the current study (family $\alpha = .92$, friends $\alpha = .93$, significant other $\alpha = .97$, and total scale $\alpha = .90$).

### 2.3.2.6 Child dependency

A Likert-style question was developed in the same format as the RSA items to assess how much the child depended on their caregiver to adhere to the recommended dietary treatment (see Appendix B2). The question consisted of two opposing statements (‘My child has managed their diet on their own’ and ‘My child has relied on me to help them stick to a
protein-restricted diet’). Participants were required to select an option box closest to the end statement that described their child best, based on the previous few weeks.

2.3.2.7 Treatment adherence

Two measures of treatment adherence were used: 1) the proportion of blood phe concentrations within target range in the preceding year, and 2) the proportion of required blood samples submitted in the preceding year. This information was extracted from the child’s existing medical records using electronic databases and patient notes. Blood samples had been routinely collected using Guthrie card blood spots or venous samples and analysed using Tandem Mass Spectrometry or Thermo High-performance Liquid Chromatography.

The three PKU clinics used the National Society for PKU recommendations (NSPKU 2014) regarding target blood phe concentrations and required frequency of blood samples. The acceptable blood phe range was 120-360 µmol/L for 0-5 year-olds, 120-480 µmol/L for over 5-year-olds, and 120-700 µmol/L for adults. However, one of the clinics accepted 100-400 µmol/L for 0-5 year-olds, 100-500 µmol/L for over 5-year-olds, and up to 700 µmol/L for adolescents (from around 14 years old). Two clinics requested weekly blood samples for 0-5-year-olds, fortnightly samples for over 5-year-olds, and monthly samples for adolescents and adults. The third clinic deviated slightly from NSPKU recommendations, requesting weekly samples for 0-2-year-olds, fortnightly samples for 25-year-olds, and monthly samples for over 5-year-olds. In addition to these minimum requirements, patients were asked to provide additional blood samples on a case-by-case basis, for example during periods of illness when phe levels can rise significantly, or to monitor metabolic control more closely when blood phe levels were high. However, the number of additional samples requested was not available from patient notes or databases.
2.3.3 Procedure

The clinical teams at the PKU clinics identified eligible caregivers by reviewing patient notes and databases. Invitation packs (including participant information sheets, consent forms and the study questionnaires) were posted to eligible caregivers (see Appendices C1-6 for materials provided to participants), who were asked to return their consent forms and questionnaires in a free-post envelope. If caregivers returned incomplete questionnaires they were contacted by phone to see if they would like to complete missing answers. An opt-out form was available for caregivers to complete if they did not want to participate, and if caregivers did not respond to their initial invitation pack, a reminder pack was sent. In addition to postal invitation, the researchers attended PKU clinics to introduce the study to caregivers and recruit participants. The study was also advertised on a poster displayed in PKU clinics, social media (Facebook), and NSPKU and clinic newsletters (Appendix D1). On return of their questionnaires, participants were given a £5 shopping voucher as a thank you for taking part. Ethical approval was granted by the NHS Greater Manchester Central Research Ethics Committee (REC reference number: 15/NW/0454), and the study was also approved by the University of Manchester Research Subcommittee, and the Manchester, Liverpool, and Bradford NHS Research and Development departments.

2.3.4 Statistical analysis

Three participants had missing answers on the GHQ-12 (1 item) and/or PIP (2-4 items), which were scored using their average scores on the relevant sub-scales. An additional participant had many unanswered items on the PIP and was therefore excluded from analyses involving this measure. The normality of the data was examined by assessing the closeness of mean and median scores, levels of skewness and kurtosis, and the similarity of the variable histograms to the normal distribution curve. All variables were normally
distributed except the MSPSS significant other subscale and the child dependency scale, which were negatively skewed.

To examine associations between demographic variables, caregiver measures, and treatment adherence, Pearson’s correlations were used for normally distributed variables and Spearman’s correlations were used for non-normally distributed variables. Multiple regression analysis was used to examine the predictors of parental psychological distress (GHQ-12 score), and exploratory regression analyses examined the predictors of parenting stress (frequency and difficulty) and treatment adherence. Using a minimum of 10 participants per predictor variable to prevent overfitting, four predictor variables were included in the regression models. For all models, Variance Inflation Factor (VIF) scores indicated that multicollinearity did not create significant bias, and the Durbin-Watson statistic indicated no significant serial correlation between the residuals. The p value was set at 0.05 for all analyses.

2.4 Results

2.4.1 Participant characteristics

Forty-six out of 192 invited caregivers participated (28/94 from Manchester, 6/44 from Liverpool, and 12/54 from Bradford). The participation rate was therefore 24%. An additional four caregivers (2% of total invited) elected not to participate via an opt-out form. Of the 46 primary caregivers, 44 were mothers (96%), one was a father (2%), and one was a grandmother (2%). Two caregivers completed the questionnaires for two siblings with PKU, and for the purposes of analysis, one child from each sibling pair was selected at random. Twenty-nine (63%) of the children were male and 17 (37%) were female. The children’s mean age was 6 years and 11 months (SD=4 years, 10 months, range=4 months-15 years, 10 months), and the caregivers’ mean age was 36 years 11 months (SD=8 years, 4 months, range=22 years-66 years, 2 months). All caregivers had English as their first
language except one mother, whose first language was Punjabi. Five caregivers (11%) did not report their highest qualification, ten reported GCSEs (22%), eight reported A Levels (17%), four Diplomas (9%), 13 Degrees (28%), five Masters (11%) and one reported a Doctorate (2%). Ten caregivers did not report their annual household income, but for the remaining 36 caregivers, their mean income was £37,157 (SD=£24,598, range=£6500-100,000).

2.4.2 Levels of distress, parenting stress, resilience, social support, and treatment adherence

The mean score on the GHQ was 13.09 (see Table 1), with 27 caregivers (59%) scoring above the clinical cut-off score of 12, indicative of levels of anxiety and depression in the clinical range. The mean care dependency score was 5.78, suggesting that on average, children were highly dependent on their carers for adhering to dietary treatment.

<table>
<thead>
<tr>
<th>Measure</th>
<th>N</th>
<th>Mean (SD)</th>
<th>Range</th>
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<tbody>
<tr>
<td>GHQ-12</td>
<td>46</td>
<td>13.09 (5.09)</td>
<td>5-27</td>
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<tr>
<td>PIP Total Frequency</td>
<td>45</td>
<td>102.04 (25.92)</td>
<td>50-158</td>
</tr>
<tr>
<td>PIP Total Difficulty</td>
<td>45</td>
<td>99.98 (30.79)</td>
<td>45-169</td>
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<tr>
<td>RSA</td>
<td>46</td>
<td>167.46 (24.12)</td>
<td>114-227</td>
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<tr>
<td>MSPSS friend</td>
<td>46</td>
<td>19.61 (6.62)</td>
<td>4-28</td>
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<tr>
<td>MSPSS family</td>
<td>46</td>
<td>20.93 (5.78)</td>
<td>7-28</td>
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<tr>
<td>MSPSS sig. other</td>
<td>46</td>
<td>21.57 (7.51)</td>
<td>4-28</td>
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<tr>
<td>MSPSS total</td>
<td>46</td>
<td>62.11 (14.785)</td>
<td>27-84</td>
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<tr>
<td>Care dependency</td>
<td>46</td>
<td>5.78 (2.086)</td>
<td>1-7</td>
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<tr>
<td>% phe in target</td>
<td>46</td>
<td>69.09 (23.992)</td>
<td>0-100</td>
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<tr>
<td>% blood samples</td>
<td>46</td>
<td>107.17 (60.484)</td>
<td>8-333</td>
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</table>
2.4.3 Associations between demographic variables, caregiver measures, and treatment adherence

Caregiver psychological distress and stress related to caring for a child with an illness were strongly and negatively associated with caregiver level of resilience (see Table 2). Furthermore, levels of psychological distress and parenting stress were closely and positively correlated with one another. Conversely, level of psychological distress was not significantly associated with perceived social support, child dependency, or demographic factors (caregiver and child age, caregiver qualifications, and household income).

Whilst caregivers’ stress related to caring for a child with an illness (both frequency and difficulty) was moderately and negatively associated with their perceived support from friends, it was not significantly correlated with their perceived support from family or significant other. Additionally, although their level of child dependency was moderately and positively associated with their stress difficulty score, it was not associated with their stress frequency score. Finally, stress was not significantly associated with demographic factors.

Regarding treatment adherence, the percentage of blood phe concentrations in target range was moderately negatively correlated with parent and child age and moderately positively correlated with caregivers’ perceived support from family. However, it was not significantly associated with caregivers’ perceived support from friends or significant other, child dependency, resilience, psychological distress, stress related to caring for a child with an illness, or other demographic factors. Finally, whilst the percentage of blood samples submitted was moderately, negatively associated with the proportion of blood phe concentrations in target range, it was not associated with any other variables.
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<td>2. Child age</td>
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<td>3. Parent qualification</td>
<td>.20</td>
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<td>4. Parent income</td>
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<td>.15</td>
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<td>5. MSPSS total</td>
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<tr>
<td>6. MSPSS friend</td>
<td>.15</td>
<td>.27</td>
<td>-.11</td>
<td>.12</td>
<td>.72**</td>
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<td>7. MSPSS family</td>
<td>-.08</td>
<td>-.04</td>
<td>-.18</td>
<td>-.04</td>
<td>.71**</td>
<td>.30*</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. MSPSS sig. other</td>
<td>-.18b</td>
<td>-.26b</td>
<td>.14b</td>
<td>.57**b</td>
<td>.76***b</td>
<td>.34b</td>
<td>.42**b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Child dependency</td>
<td>-.34ab</td>
<td>-.63***b</td>
<td>.06b</td>
<td>-.09b</td>
<td>-.28b</td>
<td>-.45**b</td>
<td>-.19b</td>
<td>-.02b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. RSA total</td>
<td>.09</td>
<td>.11</td>
<td>.17</td>
<td>.21</td>
<td>.52**</td>
<td>.41**</td>
<td>.30*</td>
<td>.40**b</td>
<td>-.24b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. GHQ-12</td>
<td>-.06</td>
<td>-.05</td>
<td>.18</td>
<td>.01</td>
<td>-.19</td>
<td>-.16</td>
<td>-.09</td>
<td>-.16b</td>
<td>.16b</td>
<td>-.54**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. PIP frequency</td>
<td>.08</td>
<td>-.08</td>
<td>.03</td>
<td>-.16</td>
<td>-.30*</td>
<td>-.37*</td>
<td>-.18</td>
<td>-.21b</td>
<td>.27b</td>
<td>-.62**</td>
<td>.51**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. PIP difficulty</td>
<td>-.04</td>
<td>-.14</td>
<td>.04</td>
<td>-.24</td>
<td>-.29</td>
<td>-.39**</td>
<td>-.2</td>
<td>-.16b</td>
<td>.30**b</td>
<td>-.63**</td>
<td>.55**</td>
<td>.93**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. % phe in target</td>
<td>-.36*</td>
<td>-.38**</td>
<td>-.13</td>
<td>-.03</td>
<td>.11</td>
<td>-.16</td>
<td>.43**</td>
<td>.19b</td>
<td>.19b</td>
<td>-.04</td>
<td>-.09</td>
<td>-.10</td>
<td>-.08</td>
<td></td>
</tr>
<tr>
<td>15. % blood samples</td>
<td>.14</td>
<td>.13</td>
<td>.15</td>
<td>-.02</td>
<td>.13</td>
<td>.26</td>
<td>-.04</td>
<td>-.02b</td>
<td>-.20b</td>
<td>.17</td>
<td>-.10</td>
<td>.04</td>
<td>.06</td>
<td>.43**</td>
</tr>
</tbody>
</table>

Note: *p<.05, **p<.01; b = Spearman’s rho correlation, all other correlations are Pearson’s
2.4.4 Predictors of psychological distress, parenting stress, and treatment adherence

Due to the number of significant correlations found, a multiple regression analysis was used to examine the best predictors of parental psychological wellbeing using the variables that were hypothesised to influence GHQ-12 score (Table 3). Given the high correlation between parenting stress frequency and difficulty scores (r=.93), only one was used (PIP difficulty).

Table 3. Multiple regression analysis using parenting stress, resilience, social support, and child dependency to predict caregiver psychological distress

<table>
<thead>
<tr>
<th>Criterion variable: GHQ total score</th>
<th>Enter</th>
<th>B</th>
<th>SE B</th>
<th>Finalβ</th>
<th>p</th>
<th>R²</th>
<th>F change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenting stress: difficulty</td>
<td>Parenting stress: difficulty</td>
<td>.061</td>
<td>.027</td>
<td>.366</td>
<td>.032</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resilience</td>
<td>Resilience</td>
<td>-0.08</td>
<td>.039</td>
<td>-.371</td>
<td>.049</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social support: total</td>
<td>Social support: total</td>
<td>.035</td>
<td>.051</td>
<td>.101</td>
<td>.497</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child dependency</td>
<td>Child dependency</td>
<td>.145</td>
<td>.341</td>
<td>-.060</td>
<td>.673</td>
<td>.367</td>
<td>5.791**</td>
</tr>
</tbody>
</table>

Note: F change *p<.05, ** p<.01

When parenting stress, resilience, perceived social support, and child dependency were entered simultaneously, the regression model explained 36.7% of the variance in level of psychological distress. However, whilst caregivers’ parenting stress and resilience both explained significant, independent variance (Finalβs=.366 and -.371, respectively), their perceived social support and child dependency did not.

Exploratory regression analyses were used to examine predictors of parenting stress (frequency and difficulty) and the proportion of blood phe concentrations within target range (Table 4). When examining predictors of parenting stress, given the close relationship between child dependency and age (Spearman’s Rho=-.63), age was entered first to determine whether child dependency could explain additional variance. Perceived support
from friends was entered rather than total social support due to its closer correlation with parenting stress.
Table 4. Hierarchical regression analyses predicting parenting stress (difficulty and frequency) and the proportion of blood phe concentrations within target range

<table>
<thead>
<tr>
<th>Criterion variable: PIP Difficulty</th>
<th>Enter</th>
<th>B</th>
<th>SE B</th>
<th>Finalβ</th>
<th>p</th>
<th>R²</th>
<th>F change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age</td>
<td></td>
<td>-.875</td>
<td>.946</td>
<td>-.140</td>
<td>.360</td>
<td>.019</td>
<td>.855</td>
</tr>
<tr>
<td>2. Age</td>
<td></td>
<td>.536</td>
<td>.988</td>
<td>.086</td>
<td>.590</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social support: friends</td>
<td></td>
<td>-.649</td>
<td>.638</td>
<td>-.138</td>
<td>.316</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resilience</td>
<td></td>
<td>-.677</td>
<td>.177</td>
<td>-.522</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child dependency</td>
<td></td>
<td>2.495</td>
<td>2.528</td>
<td>.170</td>
<td>.330</td>
<td>.435</td>
<td>7.713**</td>
</tr>
</tbody>
</table>

| Criterion variable: PIP frequency |
|-----------------------------------|-------|-----|------|--------|------|-----|----------|
| 1. Age                            |       | -.413 | .802 | -.078  | .609 | .006| .265     |
| 2. Age                            |       | 1.014 | .833 | .192   | .231 |     |          |
| Social support: friends           |       | -.537 | .539 | -.136  | .324 |     |          |
| Resilience                        |       | -.538 | .149 | -.493  | .001 |     |          |
| Child dependency                  |       | 3.062 | 2.133| .248   | .159 | .433| 7.642**  |

| Criterion variable: % of blood phe concentrations in target range |
|---------------------------------------------------------------|-------|-----|------|--------|------|-----|----------|
| 1. Age                                                        |       | -1.879 | .683 | -.383  | .009 | .147| 7.571**  |
| 2. Age                                                        |       | -1.249 | .835 | -.255  | .143 |     |          |
| Social support: family                                         |       | 1.844  | .547 | .444   | .002 |     |          |
| Parental wellbeing                                             |       | -.432  | .612 | -.092  | .484 |     |          |
| Child dependency                                               |       | 2.02   | 2.01 | .176   | .321 | .341| 5.309**  |

| Criterion variable: % of blood phe concentrations in target range |
|---------------------------------------------------------------|-------|-----|------|--------|------|-----|----------|
| 1. Age                                                        |       | -1.807 | .623 | -.368  | .006 |     |          |
| Social support: family                                         |       | 1.706  | .529 | .411   | .002 |     |          |
| Parental wellbeing                                             |       | -.320  | .601 | -.068  | .597 | .325| 6.741**  |

Note: F change *p<.05, ** p<.01
Child age did not significantly predict parenting stress related to caring for a child with an illness (frequency or difficulty). Whilst caregivers’ level of resilience explained significant variance in PIP difficulty and frequency after accounting for child age, their perceived support from friends and level of child dependency did not.

When examining predictors of the proportion of blood phe concentrations within target range, age was entered first due to the widely reported association between age and metabolic control (e.g., MacDonald et al 2010). Parent age was not selected as a predictor variable due to its high correlation with child age (r=.73). In addition, perceived support from family was used rather than total social support score due to its closer correlation with the percentage of blood phe concentrations in target range.

Child age explained significant variance in the proportion of blood phe concentrations in target range (p=0.009, r²=0.147). After accounting for child age, perceived social support explained significant additional variance, whereas caregiver psychological distress and level of child dependency did not. The inclusion of perceived support from family, parental wellbeing, and level of child dependency increased the percentage of variance explained from 14.7% to 34.1%. However, age was no longer significantly associated with the proportion in range after adjusting for the other variables (p=0.143). Due to the close correlation between child dependency and age, it was likely that they were competing in the regression model. In another model that excluded child dependency and included child age, social support from family, and parental distress (Table 4), child age and social support explained significant independent variance. The inclusion of child dependency only explained an additional 1.6% of the variance in the proportion of blood phe levels in target range (r² in the model including child dependency = .341; r² in the model excluding child dependency = .325).
2.5 Discussion

In accordance with hypotheses, caregivers had high levels of psychological distress on average, with more than half reporting levels within the clinical range. This suggests that the additional challenges related to caring for a child with PKU (e.g., around treatment adherence) affected caregivers’ mental health, which is consistent with previous findings (Gundaz et al 2015; Mahmoudi-Gharaei et al 2011).

Regarding the determinants of parental wellbeing, in line with research examining other pediatric health conditions (Cousino & Hazen 2013), increased parenting stress related to caring for a child with an illness was associated with increased psychological distress, and explained significant variance in distress levels. Similarly, increased resilience was associated with reduced psychological distress and explained independent variance. However, it is possible that these associations were bi-directional, with greater parental distress also having a negative impact on parenting stress and resilience. Resilience is defined as a good level of functioning despite psychosocial adversity (Rutter 2000), and may have helped to protect caregivers from developing poor psychological wellbeing (Hjemdal et al 2006). In contrast to studies reporting an effect of social support on parental quality of life (Fidika et al 2013; Ten Hoedt et al 2011), caregivers’ psychological distress was not associated with their perceived social support, and although increased support from friends was correlated with reduced parenting stress, it did not explain significant variance. These mixed findings may reflect the use of different outcome measures.

Research examining other pediatric conditions has reported an influence of increased parental responsibility for treatment adherence on parental psychological wellbeing (Cousino & Hazen 2013; Streisand et al 2005). However, in this study, level of child dependency on the caregiver for dietary adherence was not associated with level of psychological distress, and although it correlated with parenting stress difficulty, it was not a significant predictor when entered with other variables (child age, perceived social support
and resilience). In addition, child age and caregiver wellbeing were not significantly associated, which is congruent with Gundaz et al (2015), but inconsistent with studies reporting an association between child age and parental quality of life (Fidika et al 2013; Ten Hoedt et al 2011).

Contrary to hypotheses, caregiver levels of psychological distress, parenting stress, and resilience were not associated with treatment adherence. Whilst this contradicts associations between treatment adherence and parental wellbeing for children with other metabolic conditions (e.g., Driscoll et al 2010; MacKey et al 2014; Skocic et al 2012; Whittemore et al 2012), it is consistent with research showing no association for parents of children with PKU (Fehrenbach & Peterson 1989; Reber et al 1987). This implies that despite experiencing increased levels of psychological distress, distress did not affect caregivers’ ability to adhere to treatment.

In accordance with research indicating reduced metabolic control with age (e.g., MacDonald et al 2010), child age explained 14.7% of the variance in the proportion of blood phe concentrations within target range. However, child dependency was not significantly correlated with treatment adherence, suggesting that other factors, such as increased social pressures around food and lifestyle, might mediate the effect of age on dietary compliance (e.g., Levy & Waisbren 1994). After accounting for age, higher levels of caregiver perceived support from family predicted better metabolic control, consistent with research examining other metabolic conditions (e.g., Miller & DiMatteo 2013). It is likely that increased support from family members helps to negotiate the challenges of dietary adherence, for example, through greater assistance with meeting the child’s dietary needs and making necessary adjustments. Finally, socioeconomic factors (parent income and qualification) were not associated with parental wellbeing or treatment adherence.
2.5.1 Limitations

Whilst this study could be argued to have a small sample size, it had a reasonable response rate (24%), with recruitment from three different clinics. However, it was difficult to determine how representative the sample was of the whole patient population, because data regarding all patients (e.g., treatment adherence statistics) were not available. It is therefore possible that more caregivers with better treatment adherence or psychological wellbeing participated.

There are some limitations regarding the study measures. The study relied upon self-report questionnaire measures, and the inclusion of clinical interviews or observations may have provided more enriched data regarding psychological wellbeing. In addition, the proportion of required blood samples submitted was not an accurate estimate of treatment adherence in this study because it was not possible to obtain the number of additional samples requested. A significant correlation between the proportion of submitted samples and the proportion of phe concentrations in target range (r=-.43) indicated that more samples were requested when metabolic control was poor. This suggests that the proportion of blood samples was not a valid measure of treatment adherence. Results involving this measure should therefore be interpreted with caution. Exploratory t-tests were carried out to examine differences between children with 100% or more blood samples submitted based on minimum requirements and children with less than 100%, with results indicating no significant differences for any caregiver or demographic variable.

Due to the cross-sectional design of the study, it is difficult to establish cause and effect relationships between variables, and a longitudinal study may have enabled a more robust interpretation of causal mechanisms. Additionally, it was not possible to compare levels of psychological distress among different parent groups, because a control group of parents of healthy children was not recruited. Finally, due to the exploratory nature of the
regression analyses, with no corrections made to account for multiple testing, their findings should be interpreted with caution.

2.5.2 Implications for clinical practice

The results of this study highlight the need for clinicians to consider the psychological impact of parenting a child with PKU and to provide appropriate support to caregivers as required. This may involve referral to appropriate psychological services or to support groups, which could play an important role in relieving caregiver burden (e.g., Awiszus & Unger 1990). Whilst there is currently a lack of studies examining interventions to support parental wellbeing, the results suggest that interventions focused on reducing parenting stress related to caring for a child with an illness and building resilience could be beneficial.

With regards to promoting treatment adherence, the results suggest that interventions to promote dietary compliance may be particularly important for older children, as metabolic control decreased with age. In addition, as perceived social support from family had a significant influence, interventions targeted toward helping family members become more supportive may be particularly useful. For example, family therapy involving communication training and cognitive restructuring has been beneficial for promoting improved metabolic control for adolescents with diabetes (Wysocki et al 2006).

2.5.3 Future research

It would be useful for future research to replicate these findings with larger sample sizes and to compare levels of psychological distress between different parent groups (e.g., mothers and fathers, parents of healthy children and other health conditions, and parents of children at different developmental stages). In addition, more longitudinal and intervention studies are needed to examine causal influences on caregiver wellbeing and treatment adherence and how to promote improvements.
2.5.4 Conclusion

This study found that caregivers of children with PKU had high levels of psychological distress, and that this was influenced by their level of parenting stress related to caring for a child with an illness and their resilience. Whilst treatment adherence for children with PKU was not associated with parental wellbeing, it was associated with child age and caregiver level of perceived support from family. It is important that clinicians are aware of the psychological impact of caring for a child with PKU and provide appropriate support to caregivers. Interventions to promote treatment adherence may be of particular benefit for parents of older children, with a focus on promoting support from family members.
2.6 References


their role in adjustment to stressful life events. *Clinical Psychology and Psychotherapy* 13: 194-201.


Rutter M (2000) Resilience reconsidered: conceptual considerations, empirical findings,


of Personality Assessment 55: 610-7.
3.1 Introduction
The following paper is a critical evaluation of the systematic literature review and empirical study and how they fit within the wider literature. Reflections are made regarding the strengths and limitations of the papers, the pertinent issues that arose during design and implementation, and the personal experience of the research process.

3.2 Paper 1: Systematic literature review
3.2.1 Selecting the review question
The idea for the review initially stemmed from the aims of the empirical paper, which examined predictors of treatment adherence for children and adolescents with Phenylketonuria (PKU). When examining literature relating to this study, it became apparent that there was a gap in the review literature concerning influences on treatment adherence for young people with PKU. Furthermore, given the difficulties with maintaining treatment adherence, (e.g., Levy & Waisbren 1994; MacDonald et al 2010), an advantage of the review was that it could potentially be used to inform clinical practice.

When conducting the review, it was important to identify a sufficient number of articles to establish meaningful conclusions, and to find a balance between sensitivity (identifying all the relevant papers) and specificity (not identifying too many irrelevant papers, Dundar & Fleeman 2014). Initial scoping searches indicated that there was a feasible evidence-base, and PROSPERO (International Prospective Register of Systematic Review) searches confirmed that it was a novel review topic. It was considered whether other metabolic conditions treated by low-protein diets (e.g., maple syrup urine disease and homocystinuria) should be included; however, scoping searches indicated that very little research had examined these diagnoses. It was therefore decided that other conditions would be excluded, which helped to restrict the number of articles to a manageable amount within the available timeframe.
3.2.2 Inclusion and exclusion criteria

To provide the most comprehensive review regarding influences on metabolic control, studies examining any demographic or psychosocial factor relating to children or family members were included. Furthermore, only articles reporting a statistical examination were selected in order to identify the most robust associations with treatment adherence. Blood phe concentration is considered to be the best indicator of treatment adherence (e.g., MacDonald et al 2010) and was therefore selected as the outcome measure for the review.

Twelve articles referred to a relationship with demographic/psychosocial factors, but did not test this statistically and were therefore excluded. Consistent with the conclusions of the review (section 1.5.4), all of these twelve articles reported a deterioration of blood phe levels with increasing age (Acosta et al 2003; Ahring et al 2011; Anastasoaie et al 2008; Azen et al 1996; Cabalska et al 1996; Camfield et al 2004; Missiou-Tsagaraki et al 1988; Walter et al 2002; 2004; Weglage et al 1992; 1993; 1996). In addition to reporting a relationship with age, Walter and colleagues (2004) examined gender differences in metabolic control, and Weglage et al (1992), examined associations between socioeconomic status, maternal IQ, and metabolic control. However, the statistical analyses were not clearly reported in these studies and they were therefore excluded as they did not meet the inclusion criteria.

A potential limitation of the review regards the inclusion of only published journal articles. It is widely recognised that a publication bias exists, with studies reporting statistically significant results more likely to be published than those with non-significant findings (Song et al 2013). As a result, there might be some unpublished findings that were not included. Notwithstanding, it can be difficult to include grey literature, such as unpublished studies, conference abstracts and PhD theses, due to access difficulties (e.g., Song et al 2013), limited availability of information (e.g., only the abstract may be available), and uncertain quality due to the potential lack of a peer-review process. As the review aimed
to inform clinical practice based on robust findings, the decision was made to exclude grey literature, case series and review papers.

Another limitation concerns the inclusion criteria of articles published in the last thirty years (1985-2015). Although this might have caused some relevant articles to be excluded, this timeframe is consistent with similar reviews (e.g., Waisbren et al 2007), and enabled a manageable number of articles to be examined.

3.2.3 Search process and write-up

The selection of electronic databases was informed by those used in similar reviews (e.g., Neylon et al 2013), and the search terms were derived from the keywords of articles found during scoping searches. The initial search terms were expanded on by identifying synonyms and discussing key search terms with co-authors. In addition, truncation symbols were used to include singular/plural words, nouns/adjectives and different spellings.

To confirm the accuracy of data extraction, the first author manually checked the extracted data. Ideally, an independent researcher would have cross-checked a proportion to ensure reliability, as recommended by Fleeman and Dundar (2014); however, this was not possible within the time and resources of the thesis. Similarly, with hindsight, it would have been useful for a second independent researcher to carry out screening of titles and abstracts to ensure accuracy of the screening process.

Consideration was made to as to whether a meta-analysis would be appropriate to examine associations with metabolic control. However, given the many different concepts and measures used, with studies of varied quality, it was not feasible to do so (e.g., Bailar 1995), and hence a narrative synthesis of the evidence was performed.
3.2.4 Quality assessment

Given the diverse range of included studies, it was considered important to select a quality assessment tool that could be used for a range of methodologies. Scoping searches for relevant tools indicated two possible contenders: The Quality Assessment Tool for Quantitative Studies (Effective Public Health Practice Project; EPHPP) and the Quality Assessment Tool For Studies with Diverse Designs (QATSDD, Sirriyeh et al. 2012). The two tools were piloted on a small number of articles, which indicated that the QATSDD items allowed for a more comprehensive assessment of study quality for the included papers. The EPHPP tool was biased toward Randomised Controlled Trials and was therefore not appropriate for most of the included studies, which would have been rated as low quality.

The QATSDD has been used in a number of other systematic reviews including studies with diverse designs (e.g., Baxter et al. 2015; Gilham & Wittkowski 2015; Harrison et al. 2015), and has shown good content validity and reliability (Sirriyeh et al. 2012). However, some limitations of the tool should be noted. For example, Fenton et al. (2015) highlighted a lack of clarity regarding some item terminology and suggested that some studies could be ranked above others based on less important study features, due to no consideration of item weightings.

Although guidance notes are provided for each item, expertise regarding research methodology is required, and the interpretation of some items may hold some subjectivity. In addition, whilst the four-point rating-scale increases the sensitivity of the measure, it reduces the likelihood of strong inter-rater reliability. Nevertheless, for the 17% of papers that were rated by two researchers independently, inter-rater reliability was good (k=.71).
3.3 Paper 2: Empirical paper

3.3.1 Topic and hypotheses

The idea for the empirical paper stemmed from discussions with field supervisors and clinicians in the area regarding the psychological impact of caring for a child with PKU. It was striking to note that whilst the clinicians had recognised the need to support parents, little research had examined parental wellbeing and the factors that could support caregivers. The narrow body of evidence available to inform a therapeutic/support group for parents being developed by the Manchester clinic further highlighted this fact. Along with PKU-specific studies, the aims of the empirical paper were informed by the wider pediatric health literature. Reviewing the evidence-base indicated that parents of children with other rare metabolic conditions (Weber et al. 2012), rare inherited syndromes (Grant et al. 2013; Griffith et al. 2011), and more common metabolic conditions, such as diabetes (Almpani et al. 2014), had heightened levels of psychological distress, further indicating the potential relevance of this topic for parents of children with PKU.

When considering the predictors of parental wellbeing, literature regarding conceptual models of caregiver burden for parents of children with health conditions was taken into account (Raina et al. 2004), which indicated influences of resilience, caregiving stress, stress management, care dependency, and social support. Furthermore, in addition to PKU-specific studies, the factors selected for association with parental wellbeing were derived from research indicating an influence of pediatric parenting stress (Cousino & Hazen 2013; Lewin et al. 2005; Patton et al. 2011; Streisand et al. 2008), resilience (Hammall et al. 2014; Mednick et al. 2007), social support (Hatzmann et al. 2009; Speechley & Noh 1992; Venters-Horton & Wallander 2001), and child dependency (Cousino & Hazen 2013; Hatzmann et al. 2009; Raina et al. 2005) for parents of children with other metabolic or health conditions.

Given the widely acknowledged difficulties with maintaining treatment adherence (e.g., MacDonald et al. 2012), the initial idea was expanded upon by considering predictors
of metabolic control. Based on studies indicating an influence of parental wellbeing on treatment adherence in other metabolic conditions (e.g., Driscoll et al 2010; Skocic et al 2012; Whittemore et al 2012), the association between parental distress and metabolic control was examined.

3.3.2 Measures

When selecting study measures it was considered important to strike a balance between using enough scales to gather a broad and detailed dataset, whilst not putting too great a time demand on participants. Additionally, it was important to use well-validated and reliable measures to identify robust associations.

Due to its brief format, strong psychometric properties, and wide use in similar studies (Grant et al 2013; Kalliath et al 2004), the General Health Questionnaire-12 (GHQ12; Goldberg & Williams 1988) was used to measure parental psychological distress (anxiety and depression). The GHQ-12 has shown strong correlations with more in-depth measures of psychological wellbeing (Hardy et al 1999), and has been found to work as well as longer versions of this measure (Goldberg et al 1997). Very few studies have examined psychological difficulties, such as anxiety and depression, for parents of children with PKU (e.g., Gundaz et al 2015), with some focusing on Quality of Life (QoL) measures instead (Fidika et al 2013; Ten Hoedt et al 2011). Recent studies have expanded the QoL literature by developing a PKU-specific Health-Related QoL measure (PKUQOL; Bosch et al 2015; Regnault et al 2015), with findings indicating an emotional impact of PKU, anxiety about blood phe levels, and guilt regarding poor adherence to dietary intervention (Bosch et al 2015). Although a well-validated measure of generic psychological distress was used in this study, it may have been beneficial to examine PKU-specific anxieties more closely. For example, including the PKU-QOL questionnaire might have identified aspects of QoL that are more closely associated with increased distress on the GHQ-12. However, at the time of
study design, publications regarding the PKU-QOL measure were not yet available and so it was not possible to include this measure.

The Pediatric Inventory for Parents (PIP; Streisand et al 2001), Resilience Scale for Adults (RSA; Friborg et al 2006), and Multidimensional Scale of Perceived Social Support (MSPPSS; Zimet et al 1988), were selected due to their strong psychometric properties and extensive use in similar studies (Fredericks et al 2007; Grant et al 2013; Guilfoyle et al 2012; Lewin et al 2005; Patton et al 2011; Skok et al 2006; Streisand et al 2001; Windle et al 2011). However, although parent responsibility questionnaires had been developed for other metabolic conditions (e.g., the Diabetes Family Responsibility Questionnaire; Anderson et al 1990), a PKU-specific measure of child dependency on the caregiver for treatment adherence was not available, and therefore, the care dependency question was developed. To provide some consistency of rating scales, the care dependency question used the same formatting as the RSA items. However, some limitations of this measure should be noted. It was not piloted with a group of parents of children with PKU, and therefore its face validity was not well established. In addition, as only one question was used, it might not have been sensitive enough to pick up more subtle differences in level of care dependency. For example, separating the question into a number of more specific questions, such as asking about adherence to low protein foods in and outside of the home environment, and adherence to amino acid supplements, might have enabled more in-depth interpretation of the results.

As blood phe concentration is considered the best indicator of treatment adherence (e.g., MacDonald et al 2010), the proportion of blood phe concentrations within target range was used to measure this. Whilst other studies have used mean phe levels to assess metabolic control (e.g., Hood et al 2014; Viau et al 2011), this was not selected due to the expected rise in phe levels with age given the higher target levels for older children (NSPKU 2014). Although the PKU clinics referred to NSPKU (2014) management guidelines, two clinics strictly adhered to the recommendations, and the other was more flexible, allowing rounded-
up levels (e.g., instead of 120-360 µmol/L for 0-5 year olds, they accepted 100-400 µmol/L). Furthermore, the third clinic was more lenient with regards to older children, accepting up to 700 µmol/L for adolescents. It is likely that this was permitted given the recognised reduction in metabolic control with age (e.g., Walter et al 2004).

The reported differences in target phe levels reflect the lack of universally accepted, evidence-based recommendations, with different countries, and different clinics within countries, using varied management guidelines (Ahring et al 2009; Feilliet et al 2010). Hagedorn et al (2013) criticised the lack of universal guidelines, as it might mean that some patients receive sub-optimal levels of care, and it might be confusing for parents. Following a consensus paper involving patient and carer perspectives (Hagedorn et al 2013), the European Society for Phenylketonuria and Allied Disorders (E.S.PKU) have been working with healthcare professionals to produce the first European evidence-based guidelines for the management of PKU, due to be published in the near future.

In accordance with a number of other studies, the proportion of required blood samples submitted was selected as a secondary measure of treatment adherence (Ahring et al 2011; Durham-Shearer et al 2008; Freehauf et al 2013; Gleason et al 1992; Viau et al 2011; Walter et al 2002; 2004). However, data regarding the number of additional blood samples requested were not available from the patient databases or clinical notes and it was therefore not possible to calculate an accurate proportion of the requested blood samples submitted for each patient. Furthermore, the proportion of blood samples submitted was negatively correlated with the proportion of phe concentrations in target range, indicating that this was not a valid measure of treatment adherence. The results regarding this measure should therefore be interpreted with caution. Future studies should only include this measure if information regarding the additional blood samples requested for each patient is available.
3.3.3 Recruitment

Prior to recruitment, it was considered important to obtain the views of potential participants to check the acceptability of the study for caregivers. A summary of the study was therefore provided to the NSPKU, who reported that they felt the study goals were important and the study methodology was appropriate. The Community Liaison Group (CLG), a group of service-users and carers at the University of Manchester, were also consulted about the study, who fed back that the chosen measures and administration time were acceptable.

Given the rarity of the condition, it was anticipated that recruiting enough participants would be difficult (e.g., DeWard et al 2014). Whilst the original plan was to recruit only from the Manchester clinic, this was extended to two additional clinics to protect the aim of a large enough sample size. To further maximise recruitment efficiency, recruitment was combined with another trainee’s study (see study by Katie Carpenter), which examined parents’ qualitative experiences of caring for a child with PKU. Applications to the NHS Research Ethics Committee (REC) were carried out jointly, and liaison with the NHS Research and Development (R&D) departments and PKU clinics were divided between the trainees. Potential advantages of this approach were the reduced research burden on services and clinicians and the increased time and resources for engaging services.

In line with DeWard et al’s (2014) suggestions for boosting recruitment, significant attempts were made to liaise with PKU clinicians and families to get them on board with the study. Through discussions with field supervisors, it was indicated that close liaison with the PKU dietitians would be most beneficial given their regular and frequent contact with families. Substantial time was therefore invested in engaging dietitians, which was invaluable for developing recruitment ideas and learning more about the treatment of PKU. This approach included attending team meetings and delivering presentations. The dietitians agreed to remind parents about research participation opportunities during routine clinical
appointments and telephone calls, although it was expected that this might not always happen given the pressures of their clinical commitments.

In addition to postal invitation and attending PKU clinics, the trainees sought further options for contacting parents, and were invited to attend a social function for families of children with PKU. This was a fantastic opportunity for introducing the study to families and networking with other professionals who had contact with them, such as the company providers of low-protein and substitute food products. To raise further awareness of the research, a poster was displayed in PKU clinics, NSPKU and clinic letters, and on Facebook, to make use of the powerful nature of social media advertising (e.g., Hanna et al 2011). Whilst the study did not meet the target recruitment figure of 50 participants (see data analysis section), the total number of 46 participants was considered adequate.

3.3.4 Data analysis

The normality of the data was indicated by close mean and median scores, skewness and kurtosis values below or very near to 1, and histograms that looked approximately like the normal distribution curve. All measures, except the MPSS significant other and children dependency scales, which were negatively skewed, were normally distributed.

To account for the possibility of increased type 1 error rate when carrying out multiple regression analyses, a more stringent p-value should be used (e.g. p<.01) or the analyses should be stated as exploratory. Therefore, the regression analysis predicting parental psychological distress (GHQ-12 score) was selected as the main regression, and the others were stated as exploratory, with actual p-values reported. A consideration was made as to whether to enter age into the first block for the regression analysis predicting psychological wellbeing, given the studies indicating an association with parental quality of life (Fidika et al 2013; Ten Heodt et al 2011). However, as the evidence was mixed, with some studies reporting no association between parental distress and child age (e.g., Gundaz et al 2015), it
was determined that there was not a strong theoretical reason for doing so. Furthermore, although the target sample size was 50 participants (to allow five predictor variables), only 46 were recruited, meaning that there was insufficient power to include an additional variable to the four hypothesised predictors.

When predicting stress frequency and difficulty scores it was possible to enter child age in the first block given the sample size and predictors of interest, and furthermore, as child dependency was associated with parenting stress difficulty, it was of interest to establish whether it could explain variance after accounting for child age. In addition, given the widely reported association between age and treatment adherence (e.g., MacDonald et al 2012), age was entered as a predictor of the proportion of blood phe levels within target range, to establish whether the other variables could explain additional variance after accounting for this.

3.3.5 Limitations

A potential limitation of the study was the difficulty in determining how representative the sample was of the whole patient population, because data regarding all patients (e.g., treatment adherence statistics) were not available. The PKU clinics unfortunately did not collect routine data regarding the population, such as the number of patients with good adherence, and hence were not able to provide this. In addition, information regarding the parents who did not respond was not available, and it is therefore unknown whether parents with greater levels of psychological distress felt unable to take part, or whether more parents with poorer psychological wellbeing took part due to the study’s relevance to them. The possibility of having more participants with better treatment adherence or psychological wellbeing might therefore reduce the generalisability of the findings to other parents of children with PKU.
Another limitation concerns the difficulty with ruling out other stressors that may impact parental wellbeing. Whilst the exclusion criteria of the presence of other significant health problems or caring responsibilities that may impact parental mental health was applied, this was determined by the clinical team, who might have had limited knowledge of additional stressors. For some participants, their psychological wellbeing may have been affected by other factors, and a comparison group of parents of children with healthy children would have enabled a more enriched interpretation of the unique impact of PKU.

3.3.6 Ethical considerations
Some participants could have found the questionnaire topics to be sensitive or upsetting, and completing them may have highlighted some areas of psychological need for families. To support parents, a detailed debrief sheet (Appendix C6) was therefore distributed in the study invitation packs, which contained information for a number of support services. Parents were advised to contact their GP if they were experiencing low mood, or to speak to one of the researchers or clinical team, who could signpost them to an appropriate support service.

3.3.7 Links with the systematic literature review
The findings of the empirical paper could be used to extend the conclusions of the systematic literature review. In accordance with the review, reduced metabolic control was associated with increased child age. In addition, whilst the impact of child gender was not a focus of the empirical paper, exploratory t-tests found that psychological wellbeing and treatment adherence were not significantly different for parents of male and female children, consistent with the findings of the review.

Regarding parent factors, the lack of a significant association between parent income and metabolic control was consistent with two studies reported in the review (MacDonald et al 2008; Reber et al 1987), and in contrast to Griffiths and colleagues (2000), who found
that chief earner income was positively correlated with blood phe level. Furthermore, regarding parent educational level, although inconsistent with one study (Shulman et al 1991), the lack of an association between parent qualification level and metabolic control was consistent with the majority of studies examining this association (Alaei et al 2011; MacDonald et al 2008; Olsson et al 2007; Reber et al 1987). In conclusion, although findings were mixed, combining the results of the empirical paper and systematic literature review indicated that metabolic control may not be associated with sociodemographic factors relating to parents.

The lack of a significant association between parental distress and metabolic control is in accordance with the conclusions of the literature review, which identified two studies reporting no relationship between parenting distress or parenting-related stress and blood phe levels (Fehrenbach & Peterson 1989; Reber et al 1987). However, the moderate negative association between parent age and metabolic control in the current study is in contrast to MacDonald et al (2008), who reported no association. It is likely that parent age was associated with metabolic control due to its close association with child age, which is known to impact blood phe levels.

Finally, regarding family factors, whilst the systematic review indicated mixed findings regarding the association between family cohesion and metabolic control, no studies were identified that examined the influence of caregiver perceived social support. Therefore, the finding that higher caregiver perceived social support predicted better metabolic control, even after accounting for age, is a novel finding and area of investigation.
3.4 Future research directions

Whilst the empirical paper examined a number of factors related to parental psychological distress and treatment adherence, further research is necessary to fully understand the determinants of parental wellbeing and metabolic control. For example, it is likely that additional psychological factors play a role in determining wellbeing, such as coping style (Rao et al 2004). In addition, as qualitative studies have indicated significant emotional difficulties particularly following diagnosis (Awiszus et al 1990), and adjustment to diagnosis (Lord et al 2008), further research is needed to examine parental wellbeing for parents at different time-points. More longitudinal or cross-sectional, comparative studies with larger sample sizes are required to examine these differences.

Another important area of investigation concerns the impact of child behavioural or mood difficulties on parental distress, given the increased behavioural difficulties (Anjema et al 2011; Smith & Knowles 2000) and poorer psychological wellbeing (Brumm et al 2010; Clacy et al 2014) associated with reduced metabolic control. Building from the current research, another study is being designed by a ClinPsyD student (Olivia Ambler from Cardiff University), to examine the associations between child behavioural difficulties, parental psychological distress, parenting stress related to caring for a child with an illness, resilience, and perceived social support.

There are currently no reported interventions to improve wellbeing for parents of children with PKU, and there are few studies examining interventions for parents within the wider pediatric literature (Lohan et al 2015). Given the limited PKU-specific research, it may be useful to draw on research examining other metabolic conditions when developing interventions. Weber et al (2012) recommended a family systems illness model for guiding psychological assessment and intervention for families of children with inherited metabolic conditions, which involves utilising family strengths to promote wellbeing, in the context of individual and family lifecycle stages. Alternatively, a study by Monaghan et al (2011) found
that a telephone-based intervention, based on social cognitive theory, led to improvements in wellbeing for parents of children with diabetes. Other research has also indicated the benefits of group interventions for parents of children with metabolic conditions (Grey et al 2011; Merkel & Wright 2012), in part due to the increased opportunities for social support.

### 3.5 Personal reflection

When selecting a research topic, I was keen for the thesis to align with my clinical interest of working with children and adolescents, and to conduct research that could influence clinical practice. This topic has developed my knowledge of working with families with children with health conditions and emphasised the important role clinical psychologists have in contributing to the evidence-base. A positive outcome is that it has inspired further research in this area, namely an examination of the relationship between parental wellbeing and child behaviour.

During the research process, it was very positive to see the great interest that many participants showed in the research, and it was useful to discuss research ideas with them and learn more about their experiences. In addition, it was very useful to work alongside another trainee with regards to submitting a joint ethics application and liaising with the PKU clinics. Without being able to share this work, it would have been difficult within the timeframe to focus on recruiting from three different sites, given the rarity of the disorder and the efforts necessary to engage services.

Prior to the thesis, I had not yet conducted a systematic literature review, and I was therefore most concerned about this element. However, carrying out the review enabled me to develop new skills in this area and a greater understanding of the benefits of synthesising findings into an evidence-base. The time required to carry out different stages of the review process was initially underestimated, and retrospectively, it would have been useful to permit a greater amount of time earlier in the thesis to this. A particularly
useful stage was carrying out the quality appraisal, which highlighted the factors important for a high quality study, and which will be taken forward to future research projects.

3.6 Conclusions

The overall aim of this thesis was to examine influences on parental psychological wellbeing and treatment adherence for children and adolescents with PKU. The systematic review identified that whilst a range of demographic and psychosocial variables were associated with metabolic control, the most reproducible association was with child age. The empirical paper found that parental psychological wellbeing was predicted by parenting stress and resilience, whereas treatment adherence was predicted by child age and perceived support from family. This thesis has highlighted a paucity of research examining some influences on parental psychological wellbeing and treatment adherence, and therefore further research is required, particularly more longitudinal and intervention studies.
3.7 References


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4. Appendices

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A1 Author guidelines – Journal of Inherited Metabolic Disease

Aims and Scope
The JIMD is the official journal of the Society for the Study of Inborn Errors of Metabolism, SSIEM. By enhancing communication between workers in the field throughout the world, the JIMD aims to improve the management and understanding of inherited metabolic disorders. It publishes results of original research and new or important observations pertaining to any aspect of inherited metabolic disease in humans and higher animals. This includes clinical (medical, dental and veterinary), biochemical, genetic (including cytogenetic, molecular and population genetic), experimental (including cell biological), methodological, theoretical, epidemiological, ethical and counselling aspects. The JIMD also reviews important new developments or controversial issues relating to metabolic disorders and publishes reviews and short reports arising from the Society's annual symposia. A distinction is made between peer-reviewed scientific material that is selected because of its significance for other professionals in the field, and non-peer-reviewed material that aims to be important, controversial, interesting or entertaining (“Extras”).

Scientific contributions

Full Articles
The JIMD welcomes scientific contributions for publication as printed full articles in the following categories:

• Original Articles: Important manuscripts that may be expected to influence or change clinical or research practice with regard to inherited metabolic disorders. Original articles may include comprehensive studies on disease features in groups of patients, important novel information on a disease or relevant research findings. Exceptional case reports that are judged to be of general interest to the readers may also be accepted as original articles. The editors may reject submitted manuscripts as original articles but invite revision or resubmission for publication as Reports in “JIMD Reports”. Anecdotal observations may also be submitted as “Extras”.

• Rapid Communications: Highly competitive and timely manuscripts; please discuss this with the editors: editor@jimd.org.

• Reviews: Concise summaries of metabolic pathways, specific disorders, methods, treatment options etc.

• Metabolic Dissertations: The JIMD invites all researchers who have completed a Ph.D. or M.D. thesis in the field of inborn errors of metabolism to submit a comprehensive review of the topic of their thesis. The article should not focus solely on the research findings but should cover all relevant information in the respective field. Such reviews preferably (but not necessarily) have a single author (other contributors should be acknowledged) and will be published with a photograph of the investigator. All authors are invited to provide a colour picture that may be used for the front cover of the issue in which the article appears.
**Manuscript structure**

The first page should include:

- **Title** of the article
- **Authors’ names and institutional affiliations** set out as in a current issue of the JIMD
- Name, email address and full postal address, including postal (ZIP) code, of the author who will be dealing with correspondence and proofs.
- **Word counts** for the text (excluding summary, acknowledgments, references and figure legends) and the summary. **Number of figures and tables:** please also state whether a colour picture is provided that may be used for the *front cover of the issue in which the article appears.*

The second page should include

- A **summary** (=abstract) of not more than 250 words (Medline allows a maximum of 4096 characters and will truncate longer abstracts).
- A **concise 1 sentence take-home message** (synopsis) of the article, outlining what the reader learns from the article (this is usually printed on the (inside) back cover of JIMD)

**Recommendations for Manuscript Length**

Competition for publication in all scientific journals has become increasingly intense, and the JIMD is no exception. We strongly encourage prospective authors to consider brevity in their presentation, and if needed to avail themselves of the on-line supplementary material for those Figures and Tables that could be accommodated in that venue. In order for the Editorial Board to accommodate the broadest perspective of submissions, and to maximize the access for prospective authors to both JIMD print and On-Line JIMD reports, the following recommendations for length have been formulated:

**Full articles:** Total word count 3000, including 500 words for the Introduction and a maximum of 4 combined figures/tables.
**Reports:** Total word count 2250, including 400 words for the introduction and a maximum of 3 total figures/tables.

It is expected that more comprehensive reviews will exceed these limits, but the authors of such reviews are again encouraged to work for brevity and succinctness in presentation. In all instances, literature citations should be reasonable and appropriate for the presentation, but should not exceed 30 citations for full articles and 25 citations for reports. Appropriate use of the cited literature is one way in which prospective authors can constrain the length of their submissions.

**Units, symbols, database references**

At the time of first mention, diseases, enzymes or genes should be referenced to the appropriate classification, nomenclature or database:

- Enzymes to an Enzyme Commission (EC) number ([http://www.chem.qmul.ac.uk/iubmb/enzyme/](http://www.chem.qmul.ac.uk/iubmb/enzyme/))
- Genes to the HUGO-approved gene symbol ([http://www.gene.ucl.ac.uk/nomenclature/](http://www.gene.ucl.ac.uk/nomenclature/))
- Genetic variants to an adequate variant database (ClinVar, LOVD, etc.)
- Key words should use Human Phenotype Ontology (HPO).

Authors should use SI units throughout the manuscript. Biochemical nomenclature should follow IUPAC-IUB recommendations ([http://www.chem.qmul.ac.uk/iupac/jcbn/](http://www.chem.qmul.ac.uk/iupac/jcbn/)). Nomenclature of mutations or genetic variants should follow HGVS recommendations ([http://www.hgvs.org/mutnomen/](http://www.hgvs.org/mutnomen/)). At the time of first mention, genetic variants should be
described with both protein designation and DNA designation (based preferably on cDNA reference numbers).

References to electronic databases (e.g. OMIM disorder/gene accession number(s), EC numbers, HUGO-approved gene symbol, GenBank Accession and version number(s) of the relevant wild-type gene sequence(s), locus-specific database(s) or other URLs of relevant databases)

Previously published material should be acknowledged, and written permission from copyright holders must be obtained to reproduce figures, tables or substantial sections of text. Where a paper relies on material that is under consideration by, or in press in another journal, a copy of this must be provided for the referees.

When writing the articles, please keep in mind the broad readership of the JIMD. For example, for methods that are widely reported or published it may be worthwhile to provide a brief two to three sentence description of the protocol to provide the reader with some insight into the methods used.

References
Consult a current issue of the journal. Citations in the text should use authors’ names then the date, e.g.: (Smith and Smith 1977); for 3 or more authors use et al, e.g. (Jones et al 1989). The full references are listed in alphabetical order at the end of the paper. Authors are listed without ‘and’. Give the first 3 authors plus et al when there are 7 or more authors. Both in the text and list use ‘et al’ without punctuation or italicization. Journal abbreviations follow Index Medicus or Chemical Abstracts. Examples are:

Journals:

Chapter in an edited book:

To cite a web site in the text (but not a specific document), it is sufficient to give the address/URL (e.g., http://www.ssiem.org) without an entry in the reference list. However, when citing a specific web document or information, a standard citation in the text (e.g. Gaten 2000) and an entry in the reference list is required. Internet references should include the same information that would be provided for a printed source (or as much information as possible). The Web information is then placed at the end of the reference. It is important to use "Retrieved from" and the date because documents on the Web may change in content, move, or be removed from a site altogether.

Reference to personal communications requires the explicit approval of the person quoted; written confirmation must be provided. Authors - not journal editors or copy editors – are responsible for the accuracy of all references, which includes verifying the source of email communications, before citing them as personal communications in manuscripts.
B1 Demographics questionnaire

Demographic Questions

1) Please provide your contact details. Please note that the researchers may contact you in the event of any problems during data collection.

Your name: ____________________________________________________________

Your child’s name: _______________________________________________________

Address: _______________________________________________________________

________________________________________________________________________

Phone number: _________________________________________________________

Email: _________________________________________________________________

2) Your date of birth: _____________________________________________________

3) Your child’s date of birth: ______________________________________________

4) Your gender: _________________________________________________________

5) Your first language: ____________________________________________________

6) Your relationship with your child (e.g. mother, father, carer): ________________

7) Your highest qualification: _____________________________________________

8) Your average annual family income: _____________________________________

9) Your GP’s name and contact details: _____________________________________

10) Date of completion of questionnaires: _________________________________

11) Are there any serious medical problems within your family in addition to your child’s PKU? If so, please give details: ________________________________

________________________________________________________________________

12) Do you have any other significant carer responsibilities (e.g. other dependent relatives)? If so, please give details: ________________________________

________________________________________________________________________

13) Have you or your child ever taken part in any interventions for PKU other than a low protein diet with amino acid supplements? If so, please give details: 

________________________________________________________________________

14) Have you ever sought or received any psychiatric or psychological support? If so, please give details: ________________________________
B2 Child dependency question

Child Dependency Questionnaire

V1 24.4.15

Child dependency

Please think about how much your child has relied on you to help them to stick to a protein-restricted diet over the last few weeks. Please check the option box that is closest to the end statement that describes your child best.

My child has managed their diet their own.

My child has relied on me to help them stick to a protein-restricted diet.
PKU: Parenting experiences and wellbeing.

We are writing to invite you to take part in a research study being conducted at the University of Manchester with parents of children with Phenylketonuria (PKU).

There has been little research on what it is like to look after a child with PKU. It would be useful to gain more information about this so we can identify the most effective ways to support parents.

There are two parts to this study. Part 1 will investigate how parent’s wellbeing is affected and what might help to improve their wellbeing. It will also investigate some of the things that help parents and children stick to a low protein diet. Parents of children with PKU between the ages of 0 to 16 are invited to take part.

Part 2 will investigate what it’s like to parent a child with PKU under the age of 2 years old. Parents of children with PKU up to the age of 2 are invited to take part.

As you have a child with PKU between 0 to 16 years old we are inviting you to take part in Part 1. If your child is under 2 years old you will also be invited to take part in Part 2 in a separate letter.

You will find enclosed with this letter a participant information sheet, a consent form, some questionnaires, and a list of support services.

If you would like to find out more about this project, please read the participant information sheet. If you would like any further information, please phone us on ….. or email us at…..

If you would like to take part after reading the participant information sheet, please complete the enclosed consent form and questionnaires. If you would like any help with completing the questionnaires please contact us using the above contact details. Please take short breaks when filling in the questionnaires if you feel tired.

Please return the consent form and questionnaires in the addressed pre-paid envelope (no stamp is required), or hand them in to your PKU clinic reception at your next appointment.

If you would prefer NOT to take part in this project please complete and return the attached opt-out form in the pre-paid envelope, so that we do not contact you again.

We look forward to hearing from you.

Yours sincerely,

___________________________ Dr Emma Medford, Trainee Clinical Psychologist

___________________________ Miss Katie Carpenter, Trainee Clinical Psychologist
PKU: Parenting experiences and wellbeing.

**Opt out form : Part 1**

I would NOT like to take part in the above study.

You do not have to give a reason, but if you feel able to tell us why, it will help us to understand why some people choose not to take part in this type of project.

_______________________________________________________________________
_______________________________________________________________________

Name of child__________________________

Name of Parent / Carer _________________

Date ________________

**Thank you for taking the time to complete and return this form**
Dear ....

PKU: Parenting experiences and wellbeing.

We recently wrote to you to invite you to take part in a research study being conducted at the University of Manchester with parents of children with Phenylketonuria (PKU).

If you have chosen not to take part or have already returned your consent form and questionnaire pack, please ignore this letter. If not, please find enclosed with this letter additional copies of the participant information sheet, consent form, questionnaires, and a list of support services, in case you have misplaced your invitation pack and would still like to take part.

If you would like to find out more about this project, please read the participant information sheet. If you would like any further information, please phone us on ….. or email us at …….

If you would like to take part after reading the participant information sheet, please complete the enclosed consent form and questionnaires. If you would like any help with completing the questionnaires please contact us using the above contact details. Please take short breaks when filling in the questionnaires if you feel tired.

Please return the consent form and questionnaires in the addressed pre-paid envelope (no stamp is required), or hand them in to your PKU clinic reception at your next appointment.

We look forward to hearing from you.

Yours sincerely,

Dr Emma Medford, Trainee Clinical Psychologist

Miss Katie Carpenter, Trainee Clinical Psychologist
Dear Parent / Guardian,

PKU: Parenting experiences and wellbeing.

We are writing to express our thanks to you for taking part in Part 1 of the above study. Thank you very much for completing and returning your consent form and questionnaires.

Your participation is very important as it will help contribute toward our understanding of how best to support parents of children with PKU.

We have sent a £5 Amazon voucher to your email address as a thank you for taking part.

If you would like to receive a summary of the study findings, please phone us on 07555 350386 or email us at pku@manchester.ac.uk.

Yours sincerely,

Dr Emma Medford, Trainee Clinical Psychologist

Miss Katie Carpenter, Trainee Clinical Psychologist
C4 Participant information sheet

PKU: Parenting experiences and wellbeing.

Research Team: Dr Emma Medford, Miss Katie Carpenter, Dr Anja Wittkowski (University of Manchester), Dr Dougal Hare (Cardiff University), Dr Simon Jones & Dr Stewart Rust (Central Manchester University Hospitals NHS Foundation Trust)

We would like to invite you to take part in our research study. Joining the study is entirely up to you. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will answer any questions you have.

Part 1 tells you the purpose of this study and what it will involve if you take part.

Part 2 gives you more detailed information about the conduct of the study.

We recommend that you take a minimum of 24 hours to consider the information below before deciding whether to take part.

---

**Part 1**

**1.1 What is the purpose of the study?**

There has been little research on what it is like to look after a child with Phenylketonuria (PKU). It would be useful to gain more information about this so we can identify the most effective ways to support parents. This part of the study (Part 1) will investigate how parent’s wellbeing is affected and what might help to improve their wellbeing. It will also investigate some of the things that help parents and children stick to a low protein diet. Another part of the study (Part 2) will investigate what it’s like to parent a child with PKU under the age of 2 years old.

**1.2 Why have I been invited to take part in this study?**

You have been invited to take part in Part 1 because you have a child with PKU who is between the ages of 0-16.

**1.3 Do I have to take part?**

No, you do not have to take part in the study if you do not want to. Taking part in the research is voluntary; this means it is completely up to you to decide whether or not to take part. Your decision to participate in this study will not be connected to the care you and your family are receiving now or in the future. If you decide to take part and sign the consent form but change your mind later, you are free to
withdraw at any point during the study without giving a reason and without any consequence to your current or future treatment.

1.4 What will participation involve?

3) You will complete a set of questionnaires that ask about your demographic details, wellbeing, stress, resilience and support from family and friends. The questionnaires will take about 50 minutes to complete. If there are some questions that you do not wish to answer, that is fine, but we may contact you to check that you haven’t missed them out accidentally.

4) You will be provided with a pre-paid envelope to return the questionnaires, or you can hand them in to your PKU clinic reception at your next appointment.

5) We will look at relevant sections from your child’s medical records to see how many PKU clinic appointments have been attended, how many blood samples have been sent, and how much they have stuck to a low protein diet.

1.5 What are the possible disadvantages and risks of taking part?

It is possible that the questionnaires might raise issues which could be distressing to think about. A list of agencies and people you can contact is provided should you need any additional information/support.

1.6 What are the possible benefits of taking part?

There are no direct benefits of taking part but the information gained will help services to fully understand the needs of families and the demands of caring for a child with PKU. It will help to identify some of the most effective ways to support parents. This will help clinicians to develop appropriate support packages, which may help other families in the future.

1.7 Will my taking part in the study be kept confidential?

Yes. We will handle data sensitively and in confidence, and follow legal and ethical guidelines. More details are given in Part 2.
Part 2

2.1 What will happen if I do not want to carry on with the study?

You can withdraw from the study completely at any time without giving a reason and without any consequence to your family’s current or future treatment, up until the data has been analysed. When the data is analysed it will not be personally identifiable.

2.2 What if there is a problem?

It is unlikely that anything would go wrong, but if you have a concern about any aspect of the study, you should contact one of the researchers (email pku@manchester.ac.uk and phone 07555 350386) who will do their best to answer your questions. If they are unable to resolve your concern or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Co-ordinator on 0161 275 7583 or 0161 275 8093 or by email to research.complaints@manchester.ac.uk

2.3 Will my data be confidential?

i. All data which is collected about you and your child will be kept strictly confidential and only viewed by members of the research team. It will be stored securely in a locked filing cabinet at the University.

ii. Your child’s medical data will be anonymized and transferred to the university. Data will be entered onto a computer database which will be password protected and encrypted. Each participant will be assigned a number, thus names will not be entered onto the database.

iii. We will ask for details of your GP, but will not routinely contact him/her. During the study if we have any concerns about risk of harm to anyone, then we will have to contact the appropriate agency/person to provide support. If possible, we would speak to you first about this.

iv. We plan to publish the research; however names of participants will not be used.

2.4 Will I receive any payment for taking part in the study?

No, participants will not receive any payment for taking part. However, when participants return their consent form and questionnaires, we will send them a £5 shopping voucher in the post as a thank you for taking part.
2.6 Who is organising the research?

This research is being conducted as part of the Doctorate in Clinical Psychology at the University of Manchester for Trainee Clinical Psychologists/postgraduate students Dr Emma Medford and Miss Katie Carpenter. It will be carried out under the guidance of Dr Dougal Hare, Dr Anja Wittkowski, Dr Simon Jones and Dr Stewart Rust. It is funded by the University.

2.7 Where will the findings be published?

iii. We intend to publish the results in peer-reviewed journals

iv. We intend to present the results at scientific conferences

v. We may put a summary of the findings in an NSPKU (The National Society for Phenylketonuria) newsletter.

vi. Participants will not be provided with an individual summary of their results. However, we will provide participants with a summary of the overall study findings if they would like this. When we receive the questionnaires participants will be sent a thank you letter with details about how to ask for a summary of the overall study findings if they would like to.

2.8 Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, who protect the rights, safety, dignity and well-being of participants. This study has been reviewed and given a favourable opinion by the North West Greater Manchester Central Research Ethics Committee.

2.9 Who can I contact for further information?

If you would like to discuss the study or have any questions or concerns, please do not hesitate to contact a member of our research team at (email pku@manchester.ac.uk and phone 07555 350386), or Dr Anja Wittkowski, Division of Clinical Psychology, 2nd Floor, Zochonis Building, University of Manchester, Brunswick Street, Manchester, M13 9PL.

If you would like to take part please complete the enclosed consent form and questionnaires and return in the pre-paid envelope or at your next PKU clinic appointment.

You can keep this copy of the information sheet.
**C5 Consent form**

Central Manchester University Hospitals  
Bradford Teaching Hospitals  
Alder Hey Children’s NHS Foundation Trust

**CONSENT FORM**  
V1 24.4.15

**Participant ID:**______ **Title of Project:**PKU: Parenting experiences and wellbeing.

**Name of Researcher:** Dr Emma Medford & Miss Katie Carpenter

University of Manchester in collaboration with Central Manchester University Hospital  
Department of Genetic Medicine.

<table>
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<th>Please tick as appropriate</th>
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1. I confirm that I have read the information sheet dated.................... (version............) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected, up until the research data has been analysed.

3. I understand that data collected during the study may be looked at by individuals from the University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data.

4. I understand that relevant sections of my child’s medical notes will be looked at to collect data for this research. I give permission for the researchers to have access to my child’s medical records.

5. I agree to take part in the above study.

Name of child ______________________________________________

Name of Participant (Parent) ___________________ Participant Signature ______________

Date ________________
Thank you for participating in this research. We hope that you have found it interesting and have not been upset by any of the topics in the questionnaires or interview.

However, if you have found any part of this experience to be distressing there are a number of people and organisations that you can contact for support.

If you would like to speak to one of the researchers, please contact us by phone on 07555 350386 or by email at pku@manchester.ac.uk. Alternatively, you can contact Dr. Anja Wittkowski by writing to University of Manchester, Oxford Rd, Manchester M13 9PL or emailing anja.wittkowski@manchester.ac.uk.

If you feel as though you are struggling to cope, or feeling low in mood, it is important that you go to your GP for support. You can also talk to your PKU clinician who will be able to signpost you to an appropriate support service.

There are also a number of organisations listed below that you can contact.

<table>
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<tr>
<th>Organisations</th>
<th>Contact Information</th>
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<tbody>
<tr>
<td>National Society for Phenylkentonuria (NSPKU)</td>
<td>030 3040 1090, <a href="mailto:info@nspku.org">info@nspku.org</a>, <a href="http://www.nspku.org">www.nspku.org</a></td>
</tr>
<tr>
<td>Climb</td>
<td>0800 652 3181, <a href="mailto:info.svcs@climb.org.uk">info.svcs@climb.org.uk</a>, <a href="http://www.climb.org.uk">www.climb.org.uk</a></td>
</tr>
<tr>
<td>Contact a Family</td>
<td>0808 808 3555, <a href="mailto:helpline@cafamily.org.uk">helpline@cafamily.org.uk</a>, <a href="http://www.cafamily.org.uk">www.cafamily.org.uk</a></td>
</tr>
<tr>
<td>NHS Direct</td>
<td>111, Open 24 hours a day. They provide health advice and information.</td>
</tr>
<tr>
<td>Samaritans</td>
<td>0845 7909090, Open 24 hours a day. They offer confidential emotional support by telephone, email, text, letter and face to face.</td>
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Are you the parent of a child with Phenylketonuria?

We are conducting some research with parents of children with PKU. It will look at the experience of parenting and parental wellbeing. There are two components. Part 1 looks at parental well-being and what can help with this. It will also look at things that can make it easier for parents and children to stick to a low protein diet. Part 2 looks at the experience of parenting a child with PKU.

WHY? There has been little research on what it is like to look after a child with PKU. We would like to find out more about this so we can identify the most effective ways to support parents.

WHO?
- Part 1: Parents of children with PKU aged 0-16
- Part 2: Parents of children with PKU under the age of 2
- For both studies we can only include parents of children seen at Bradford, Manchester or Liverpool PKU clinics.
- Part 1 will involve completing questionnaires.
- Part 2 will involve interviewing parents about their experiences.
- Parents will receive a voucher as a thank you for taking part.

If your child is currently being seen at the Liverpool, Bradford or Manchester PKU clinics, and you would like to find out more about this study, you can contact the researchers using the following contact details:

Email:.........................
Phone:.........................

If your child attends clinics at Alder Hey, Manchester and St. Luke’s, Bradford you will receive information in the post about the studies along with details of how to take part.