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Review article

The impact of metabolic control on cognition, neurophysiology, and well-being in PKU: A systematic review and meta-analysis of the within-participant literature☆

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ABSTRACT

Phenylketonuria (PKU) is a metabolic disease where Phenylalanine (Phe) rises much above normal levels. Cross-sectional and correlational studies provide valuable information on the importance of maintaining low blood-Phe to achieve good outcomes, but they may be confounded, at least partially, by differences in participant demographics. Moreover, the effect of Phe at older ages is difficult to ascertain because of strong associations between Phe levels across ages. Within-participant studies avoid confounding issues. We have reviewed these studies.

We followed PRISMA guidelines to search the literature for studies reporting the impact of Phe changes within participants. Phe was either increased or decreased through diet relaxation/resumption or through pharmacological interventions. Forty-six separate articles reported, singly or in combination, results on cognition ($N = 37$), well-being ($N = 22$) and neurophysiological health ($N = 14$). For all studies, we established, in a binary way, whether a benefit of lower Phe was or was not demonstrated and compared numbers showing benefit versus a null or negative outcome. We then analyzed whether critical parameters (e.g., length of the study/condition for the change, size of Phe change achieved) influenced presence or absence of benefit. For a subset of studies that reported quantitative cognitive outcomes, we carried out a meta-analysis to estimate the size of change in cognitive performance associated with a change in Phe and its significance.

There were significantly more studies with benefits than no benefits, both for cognitive and well-being outcomes, and a trend in this direction for neurophysiological outcomes. The meta-analysis showed a highly significant effect size both overall (0.55) and when studies with adults/adolescents were considered separately (0.57). There was some indication that benefits were easier to demonstrate when differences in Phe were larger and achieved across a longer period, but these effects were not always consistent.

These results reinforce results from the literature by demonstrating the importance of lower Phe in children as well as in adolescents and adults, even when confounding factors in group composition are eliminated. The field would benefit from further studies where Phe levels are contrasted within-participants to ascertain how much Phe needs to be changed and for how long to see a difference and which measures demonstrate a difference (e.g., which cognitive tasks).

Contents

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Phenylketonuria (PKU) is a metabolic disorder affecting between 1 in 10,000 to 1 in 12,000 births [26,85]. Individuals with PKU have mutations in the genes which code for the enzyme phenylalanine hydroxylase (PAH) which is essential for the hydroxylation of phenylalanine (Phe) into tyrosine in the liver. Since tyrosine is a precursor of dopamine, this reduces the availability of this neurotransmitter. Moreover, large amounts of Phe in the blood stream reduce the chances of other essential amino acids such as tryptophan (a precursor of serotonin) being able to pass through the blood-brain barrier as they must compete with the Phe, leading to neurotransmitter imbalances. This, in addition to the accumulation of Phe in the brain, which is toxic for white matter, impairs brain functioning [16,92]. If left untreated, PKU causes significant neurological impairment including intellectual disability, microcephaly, seizures, and behavioural difficulties [3,16]. Fortunately, early and continuous treatment (e.g., via reducing Phe intake) prevents much of the neurocognitive damage associated with untreated PKU.

The importance of maintaining low blood-Phe levels from infancy is well documented, with several reviews reporting findings of cognitive impairments being particularly evident in individuals with poor metabolic control (see [23,27,49] for reviews). Beyond cognition, early-treated patients with PKU have been found to exhibit a number of emotional and behavioural deficits, including high levels of depression, anxiety, hyperactivity, inattention, poor self-image, withdrawal, and a lack of autonomy and drive (see [14,86,96] for reviews). Metabolic control has also been linked to these cognitive and emotional impairments (e.g., [13,18,80,93]). Finally, the high prevalence of cerebral white matter abnormalities in PKU has been recognised by several scoping reviews, with consistent findings of an association between increased blood-Phe levels and more severe abnormalities [4,37,96].

Whilst the importance of metabolic control for maintaining cognition, mental health, and brain health in children with PKU (CwPKU) has been widely accepted, the importance of maintaining low blood-Phe levels during and after adolescence is less clear. European guidelines recommend maintaining Phe levels between 120 and 360 μmol/L up to 12 years of age and < 600 μmol/L after that [97,99]. US guidelines are even more strict, recommending maintaining Phe levels <360 μmol/L throughout life (American College of Medical Genetics and Genomics, ACMG, [101]). Many individuals with PKU, however, choose to relax their treatment diet in adolescence or early adulthood so that Phe levels often exceed what is recommended. For example, Phe levels were found to remain steady in Dutch CwPKU until around 13 years of age, after which they started to increase [32] and 34% of 13–18-year-olds in the US were found to no longer attend PKU clinics [10]. Walter and White [103] reported that 30% of Phe samples were above 700 μmol/L (the target recommended at the time by the United Kingdom's National Society for Phenylketonuria or NSPKU) in children younger than 10 years, but this figure rose to 80% in people aged 15 and older, with levels reaching a mean of 800 μmol/L by the age of 15 and increasing after that [103]. A clearer understanding of the potential impact of reduced metabolic control throughout the lifespan, therefore, is needed. This will allow clinicians to provide their patients with the necessary guidance to make an informed decision about continuing, relaxing or abandoning their treatment diet post-childhood. Also, the parameters of blood-Phe required to maintain optimal cognitive, emotional, and neurophysiological health in children and adults with PKU, are unclear, as well as the extent to which damage caused by excessively high levels can be reversed.

Most of the existing evidence on the importance of metabolic control comes from studies which have used either a correlational methodology or a contrast between groups of participants with high vs. low metabolic control. The problem with these studies is that variability in cognition, emotional health and brain health will be determined, not only by metabolic control, but also by individual differences in genetic endowment, educational opportunities, socio-economic status, etc., which are difficult to control. Within-participant study designs offer a gold-standard way to overcome these limitations, but results from the literature are limited. The aim of this paper is to carry out a systematic review of studies which have used a within-participant design to see whether results can be accrued in a meaningful way. Before detailing our aims and methodology, however, we will briefly review existing evidence from studies using between-participant designs. We will concentrate, in particular, on evidence regarding levels of Phe that can be considered safe. We will review evidence in the cognitive, well-being and neurophysiological domains.

Studies involving both children and adults with PKU have found worse performance in groups of individuals with higher Phe levels, but interpretations are limited by the fact that different criteria have been used for group selection. Studies considering IQ in CwPKU have reported impaired intelligence in groups with average Phe levels between 800 μmol/L and 1300 μmol/L [8,52,89,102]. In other cognitive domains, performance has been found to be impaired at lower Phe levels. For example, Schmidt et al. [83] found that, in CwPKU, 1–9 year-olds with mean blood-Phe levels **>620 μmol**/L were more impaired in sustained attention and calculation than children with mean Phe **≤240 μmol**/L. Similarly, Huijbregts et al. [54] found that 7–14 year-olds with blood-Phe levels **>360 μmol**/L made more errors in focussed attention tasks and were slower at feature identification than children with mean Phe **≤360 μmol**/L. Waisbren et al. [102] looked at correlations between IQ and childhood blood-Phe levels across 40 different studies. Meta-analytic results showed significant correlations between IQ and blood-Phe levels within the first 12 years of life, with each increase in blood Phe of 100 μmol/L during this age range predicting a decrease in IQ of 1.9 to 4.1 points. Concurrent blood-Phe levels equally correlated significantly with IQ, with each increase of 100 μmol/L predicting a drop in IQ of 0.5 to 1.4 points, (over a range of Phe from 394 to 666 μmol/L in the studies included in the meta-analyses).

Between-subject studies with adults and adolescents with PKU (AwPKU) suggest that they may be able to maintain higher blood-Phe levels than children without compromising cognitive abilities. Romani et al. [81] assessed cognitive impairment in 56 early-treated AwPKU, and found that maintaining Phe levels **<600 μmol/L** post-childhood reduced the risk of cognitive impairment in this cohort by approximately 30%, with AwPKU with current levels below this threshold demonstrating little to no cognitive impairment. Analyses of the impact of childhood Phe levels on adult outcomes, meanwhile, found a lower threshold of 360 μmol/L, after which cognitive impairments became apparent. Romani et al. [80], compared performance in AwPKU with mean adult blood-Phe levels of **>950 μmol/L**, to those with mean levels of **<650 μmol/L**, and reported differences across a range of tasks including

differences in executive function (excluding inhibition), and in measures of visuo-spatial attention, short-term/working memory, sustained attention, written and spoken language, and verbal memory and learning. When compared to controls, those with Phe **<650 μmol/L** showed a modest, but still significant, impairment. Furthermore, this study found that both lifetime and concurrent adult Phe levels were correlated significantly with performance on most tasks (excluding inhibition, short-term memory, and language tasks).

However, Jahja et al. [56] reported differences in performance between groups of AwPKU contrasting at lower Phe levels. AwPKU with lifetime Phe **≥360 μmol/L** performed worse than both controls and AwPKU with Phe **<360 μmol/L** in working memory and sustained attention. Moreover, concurrent blood-Phe levels correlated with slower performance in several tasks, including a feature integration task (all conditions), a memory search task (high working memory condition only), and a sustained attention dots task. Lifetime Phe also correlated negatively with accuracy in the high working memory load condition of the feature integration task. Finally, Aitkenhead et al. [2] assessed correlations between metabolic measures and performance in several cognitive tasks in a sample of 154 early-treated AwPKU with Phe levels ranging from 200 to 800 μmol/L. They found that performance on digit symbol coding was best predicted by concurrent Phe, with a decrease of 1.05 SD for every increase of 1000 μmol/L. This test requires participants to write down symbols under corresponding digits following a key, and it assesses a variety of skills impaired in PKU including speed of processing, visuo-motor coordination, and working memory. Importantly, correlations with concurrent Phe were maintained even when Phe levels at previous ages were taken into consideration. Similarly, a task involving learning of lists of words was best predicted by concurrent Phe, although this contribution did not remain significant when Phe at previous ages was taken into consideration. These findings suggest that, even in adulthood, maintaining Phe at lower levels is beneficial for certain domains.

Metabolic control has also been found to influence emotional well-being. For example, Smith et al. [88] measured behaviour in 544 early-treated, 8-year-old CwPKU by asking school teachers to assess the frequency of abnormal behaviours using the Rutter Behaviour Questionnaire. Those with good metabolic control (average levels **<600 μmol/L**) had fewer problems than those with worse control (**>600 μmol/L**) although they were still impaired compared to healthy controls (1.6 vs. 2.2. times more likely to show deviant behaviours). Relaxing dietary control in childhood has also been reported to impact well-being later in life. Koch et al. [60] reported more well-being difficulties (including phobias and depression) in AwPKU who had discontinued their diet aged 10, compared to those who were still following the diet, with 8/58 participants who were off-diet suffering from hyperactivity and 11/57 from lethargy. No such symptoms were reported by the nine participants who remained on diet. These findings support those of Holtzman et al. [52], who found a significant correlation between the age at which participants lost dietary control (defined as levels reaching **908 μmol/L),** and higher behaviour problem scores.

With regards to well-being in adulthood, Jahja et al. [57] found that increased depressive and avoidant personality traits in AwPKU compared to controls were only apparent when lifetime blood-Phe level was **≥ 360 μmol/L**, with no significant correlation found with concurrent blood-Phe. Burton et al. [20] reported higher levels of psychiatric distress in children, adolescents, and adults with PKU with higher median Phe and concurrent Phe, (**582** and **683 μmol/L** respectively) compared in those with lower levels (**354** and **442 μmol/L**). These findings suggest that negative effects on well-being may become apparent as soon as levels rise above 350-400 μmol/L. However, other studies have reported no effect, or a negative effect, of metabolic control on emotional well-being (e.g., [2,18,75,77]). These contrasting findings may reflect the fact that following a PKU diet may have mixed effects because, on the one hand, reduced Phe will improve brain health with positive effects on well-being but, on the other hand, following a strict diet may be stressful and unsociable, causing emotional difficulties.

Finally, outcomes in PKU can be measured in terms of brain abnormalities and neurological symptoms beyond cognitive impairments. White matter pathology has been commonly observed in people with PKU, with significant associations with elevated Phe levels reported across all ages (for studies with adults only see [29,47,73]; for studies with mixed cohorts see [46,72,95]). For example, Thompson et al. [95] assessed white matter changes in early-treated ($N = 25$) and late-treated ($N = 9$) adults and children with PKU aged 8 to 33 years who had been treated until a minimum age of 7 years and found that, when other factors in the model were controlled for, the likelihood of more severe MRI abnormalities increased 1.5 times for every 100 μmol/L rise in concurrent blood-Phe levels, and 1.3 times for every additional year off a low-Phe diet (current Phe range: 350–2000 μmol/L). Mastrangelo et al. [72] reported that, in AwPKU with concurrent Phe levels ranging from 148 μmol/L to 1900 μmol/L, each increase in blood-Phe of 100 μmol/L was associated with a 0.46 increase in participants' white matter severity score.[1] Use of modern neuroimaging techniques, such as diffusion kurtosis imaging (DKI) have further expanded our understanding of the impact of PKU on white matter integrity. With this technique, Hellewell et al. [47] reported findings of subclinical white matter abnormalities in AwPKU, as well as a significant relationship with metabolic control, with AwPKU with lower adult Phe levels demonstrating more preserved white matter microstructure (mean lifetime Phe 461 vs. 609 μmol/L; mean adulthood Phe 487 vs. 1645 μmol/L). Importantly, there were suggestions that white matter damage mediates cognitive impairments. In a 3-year longitudinal study, Hawks et al. [46] using DTI and MRI found different trajectories of white matter development in 35 participants with PKU aged 7–21 years compared to controls, as well as whole-brain and regional white and grey matter abnormalities. Importantly, mediation analyses found that whole-brain diffusivity, as well as regional diffusivity in the corpus callosum and centrum semiovale, mediated the relationship between metabolic control and executive functioning.

Neurological symptoms beyond cognitive impairments involve mainly motor and visual disturbances (e.g., tremors, motor stereotypies, tics, epilepsy, blurred vision). These symptoms occur often in untreated people with PKU (see [70]), but also, occasionally, in early-treated people (e.g., see [42], who found respectively in early- vs. late-treated % – epilepsy: 1.1% vs. 31%; tremor: 12% vs. 93%; clumsiness: 11% vs. 90%). White matter abnormalities and neurological symptoms were present in 97% of late-treated participants, and in 25% of early-treated participants [42]. Other studies have reported cortical blindness and vision loss associated with periventricular white matter and cortico-subcortical occipital lesions, and neuromyelitis optica[2] in early-treated AwPKU [7,82]. Importantly, when these symptoms appear later in life they have been found to regress or ameliorate after the reintroduction of a PKU diet, or after introduction of a PKU diet in a few cases of participants with missed diagnosis who had never been on diet (see [58]).

To summarize, cross-sectional and correlational studies provide valuable information about associations between blood-Phe levels and outcomes in PKU. However, this evidence suffers from several limitations. Firstly, it is difficult to derive conclusions about the Phe levels which are safe at different ages because of the differences in the cut offs used by different studies to compare participants with good vs. poor metabolic control. Secondly, between-group comparisons may be confounded by differences in demographics and other individual variables. For example, AwPKU and parents of CwPKU with better metabolic control may have more education and a higher socio-economic status

[1] WMSS - see [63]; Severity scores 0–4 points for increasing T2 signal alterations, plus 1 point for each location, plus 1 point for presence of patchy lesions, plus 1 point for decreased T1 signal.

[2] A demyelinating autoimmune inflammatory process affecting the central nervous system

than those with worse control (for evidence in this sense see [25,60,69]). Therefore, better cognition, and possibly better mental health and brain health, could reflect a more stimulating environment instead of (or in addition to) better metabolic control (but for evidence of effects of Phe controlling for education see [24,81]). As another example, sensitivity to Phe can vary from one individual to the next, and this may increase noise in correlational and between-groups studies (e.g., some individuals with untreated PKU seem to escape the worse effects of Phe; see [98] for a review). Thirdly, comparisons between participants with PKU and healthy controls do not account for differences caused by living with a chronic disease (such as perceived social exclusion or the stress of arranging to eat special foods) and/or the potential nutritional deficiencies caused by a PKU diet which can contribute to poor outcomes beyond high Phe levels. Finally, between-participant studies do not address the question of the extent to which existing deficits are reversed or exacerbated by changes in Phe and provide little insight into additional factors (e.g., length of treatment, magnitude of metabolic change) that contribute to the likelihood of observing changes in outcome.

Within-participant studies offer the ideal conditions for addressing questions related to the effects of changes in Phe, while at the same time controlling for any confounding individual variables. Studies of this type are limited in number and have used participants with different levels of Phe at different times. However, carrying out a systematic review can both accrue results, and capitalise on between-study differences in metabolic levels to provide evidence for the levels at which Phe becomes detrimental, and for the differences in Phe able to produce a difference in outcomes. One can carry out correlations between Phe variables and outcomes but also compare the parameters of studies where differences in Phe did, or did not, produce differences in outcomes. In particular, one can compare baseline Phe and differences in Phe. This will provide us with some indication of the parameters within which Phe manipulations can be effective.

Whilst several scoping and systematic reviews of cross-sectional studies exist, no systematic comparisons of within-participant effects of altering Phe levels have been carried out so far. We reviewed within-subject studies reporting cognitive, well-being, and/or neurophysiological outcomes in early- and late-treated children, adolescents, and adults with PKU, whose blood-Phe levels changed through dietary or pharmaceutical intervention. We wanted to establish, first, whether increasing or decreasing Phe had significant effects, respectively worsening, or improving outcomes and whether this was true both in child and adult samples. Additionally, we wanted to assess how effects were related to metabolic parameters, both by carrying out correlations, and by comparing the parameters of studies which did/did not find significant effects. For well-being and neurophysiological/neurological outcomes we could only carry-out systematic reviews and provide descriptive statistics of results since it was not possible to accrue results in a quantitative way. However, this was possible for a subset of the studies reporting cognitive outcomes and a meta-analysis was carried out on this subset.

1. Method

Where applicable, our review was conducted in adherence with the updated guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement [74].

1.1. Literature search

A literature search was conducted using the Web of Science, PubMed, Cochrane Library and PsychArticles databases (from inception to August 2022). Abstracts, titles, and author keywords were searched with the combination of terms:

PKU OR Phenylketonuria.

AND Phe OR Phenylalanine OR metaboli*.

AND manipulat* OR load* OR diet* OR pharmacolog* OR interven* OR treat* OR restrict* OR resum*.

'*' functions as a wildcard symbol to broaden the search by finding words that start with the same letters.

The inclusion criteria for a study were that it:

1) Included human participants with phenylketonuria (children, adolescents, or adults; classical or mild PKU);
2) Changes in participants' blood-Phe concentrations either through termination, relaxation, resumption, or restriction of a low-PKU diet, or through pharmacological interventions (e.g., treatment with BH4, Pegvaliase, Phe loading); we included both longitudinal studies and 'proper' intervention studies;
3) Included post-change cognitive, well-being, or neurophysiological results;
4) Included baseline and/or post-change blood-Phe levels;
5) Was written or available in English.

The exclusion criteria for a study were that it:

1) Was a review, meta-analysis, or conference abstract;
2) Phe change observed over an average period of >4 years to limit the impact of more general long-term influences.

Titles and abstracts of returned papers were initially screened by the first author to exclude duplicate and clearly ineligible studies. After the initial screening, all retrieved papers were read in full. Further references were obtained from the reference lists of reviews and relevant papers.

From the selected papers, the following data were extracted for the PKU groups:

1) Type of intervention: dietary or pharmacological;
2) Number and age of participants;
3) Age at initiation and termination of treatment;
4) Length of study-related Phe change – this is the time span over which the change in Phe was achieved;
5) Blood Phe concentrations pre- and post-change, and average difference between these two measures;
6) Outcome measures: cognitive, well-being, and neurophysiological (including neurological symptoms other than cognitive), at baseline and post Phe change.

All studies were checked for inclusion criteria and data extraction by the third author.[3]

Where papers did not include all data of interest, we included all papers that met a minimum information requirement of number of participants, age, Phe pre and/or post change, and outcome(s) in at least one cognitive, neurophysiological, or well-being domain. Where articles compared outcomes in two or more different Phe conditions (e.g., increasing and decreasing Phe) or outcomes from different domains (cognitive, well-being, or neurophysiological), these were considered separately as individual 'studies'. When only results in graph format were available, we used digitization software (PlotDigitizer) to calculate actual scores. Where blood Phe concentrations were given in mg/L or % mg, these were converted into μmol/L. Where the range of blood-Phe concentrations was given instead of the standard deviation, standard deviations were approximated using sd = (maximum-minimum)/4.

[3] The study by Ficicioglu et al. [38] was not included in our review because, although it aimed to reduce Phe level through the introduction of sapropterin, it was not successful in this endeavour as the five participants did not show any decrease in Phe level before/ after sapropterin.

1.2. Data analyses

Most studies reported well-being or neurophysiological health outcomes only in qualitative terms or in varied formats which did not allow quantitative aggregation. The same was true for a number of studies reporting cognitive outcomes. In these instances, we computed descriptive statistics in terms of number of studies showing a benefit of lower Phe levels vs. those showing no benefit or an effect in the opposite direction. Studies were defined as showing a benefit if changes in outcomes were all in the expected direction or, when changes were in both directions, if significant changes were only in the expected direction or, when statistical analyses were not reported, if positive changes were reported for at least 50% of participants and changes in the opposite direction for <20% of participants.

We ran different types of analyses. We compared numbers of studies showing benefit vs. no benefit for each outcome type (cognitive, well-being, neurophysiological) using χ^2 tests. We assessed differences between the parameters for studies showing or not showing benefits using univariate analysis of variance; and we assessed whether size of Phe-difference and/or length of study/condition predicted outcomes using binomial logistic regression. It is unclear whether results are better reflected by considering arithmetic averages or averages weighted by number of participants. Weighted averages favour large studies, which are more trustworthy, but underestimate the information provided by smaller studies which give converging sources of information from different paradigms/groups of participants. Arithmetic means have the opposite advantages and disadvantages: they properly consider results of diverse studies but fail to give more weight to studies with more participants. Therefore, we have analyzed results both using arithmetic averages and weighted averages, but taking care, in this last case, not to inflate results. This was managed by ensuring degrees of freedom reflected number of studies and not number of participants. If convergence is achieved with different analyses this will increase our confidence.

Finally, for the subset of cognitive studies which reported quantitative data, we computed effect sizes and ran a meta-analysis of those.

1.2.1. Meta-analysis

We standardised differences in performance before and after changes in Phe using Hedge's g effect sizes (ESs). A Hedges' g ES is computed by dividing the difference in measures taken before and after a change in Phe by the pooled standard deviation of the two conditions and then applying a correction for small sample sizes:

$$\text{Hedges' g} = \left(\frac{\overline{y}_{low} - \overline{y}_{high}}{s_p}\right) \times \left(1 - \left(\frac{3}{4(df) - 1.}\right)\right)$$

where '$\overline{y}_{low}$' is cognitive performance when Phe is low; '$\overline{y}_{high}$' is performance when Phe is high; 's_p' is the pooled standard deviation calculated as $\sqrt{\frac{1}{2}\left(s^2_{low} + s^2_{high}\right)}$; 's' is the SD of each condition; and n is the number of participants. *Df* is an estimate of the degrees of freedom from Pustejovsky [79]:

$$\frac{2(n-1)}{1+r^2}$$

To make sure that positive effect sizes always reflected a benefit of lower Phe, we subtracted outcomes in high Phe conditions from outcomes in low Phe conditions and then multiplied the effect size by −1 when higher values indicated worse performance (e.g., error or RT measures). Thus, positive ESs always reflected better performance in the low-Phe condition.

The meta-analysis derived a weighted, cumulative ES for change in cognitive performance after a change in Phe and assessed its significance. Individual ESs were entered into a mixed-effect meta-analysis. The model included random effects for 'study' and 'measure' nested within study. This accounted for studies where the same cohort of participants was tested with different tasks (or measures). A random effects model was appropriate because we assumed that the cumulative effect size reflected a *population* of effects which differed depending on the characteristics of the PKU group tested and the type of cognitive measure used. In contrast, a fixed effects model would assume that variation is solely due to random error (see [55] for a detailed account of fixed vs. random effects models in meta-analyses). Finally, since results were within-participants, the Phe conditions are, by definition, not independent of each other. Because the correlation between pre and post Phe-change measures could influence the estimate of the variance of effect sizes, we included a term for the correlation between measures (see [79], citing [109]). Pre/post correlations were typically not reported in the studies we reviewed, so we ran a sensitivity analysis with estimated correlations of 0.2, 0.5, and 0.8 (see [48]). If our estimate of the ES was relatively insensitive to different levels of correlation, this reassured us of the stability of our estimate.

With all meta-analyses there is a risk of a publication bias inflating the estimated ES [9]. The 'file drawer problem' is a label for the tendency not to publish non-significant findings, or findings in the direction opposite from those expected. This is more likely for studies with small samples. We assessed the potential influence of a publication bias through a funnel plot and the influence of small studies through a sensitivity analysis. The funnel plot plotted ESs on the x-axis and a measure of precision (in our case, sample sizes) on the y-axis, with high precision at the top. This should produce a plot with a funnel shape because ESs should cluster tightly around the estimated mean at the top, where the sample size is large and precision is high, and distribute more widely at the bottom, where measures have less precision. If there is no publication bias, ESs should be distributed *symmetrically* around the mean, even when sample sizes are small. In the case of publication bias, instead, there may be more measures from small studies on the positive side of the mean, with missing studies on the other side. Funnel plots often use standard error as a measure of precision, but, in our case, the number of participants is more appropriate since standard errors can be affected by variability in metabolic control which could have a larger range in larger studies. Thus, a smaller standard error may not automatically signal a more precise estimate of population values.

A sensitivity analysis (or cumulative meta-analysis) assessed whether our cumulative estimate of ES was influenced by studies with small samples (see [110]; Chapter 30, p. 288). In this analysis, we ordered our ESs according to the number of participants and subdivided them into bins. The first bin included the largest studies and the following bins added progressively smaller studies. There were six bins, with each bin adding 4 studies. If effects were unduly biased by small sample studies, the cumulative effect size should increase as smaller studies are added. Instead, if the effect size stays the same or gets smaller, we can be confident that the estimate is not inflated by small samples or publication bias (see logic outlined in Borenstein, et al., 2009, Chapter 30).

2. Results

The initial keyword search yielded 4620 results. 1571 were excluded as duplicates and a further 2914 were excluded through inspection of titles and abstracts. The remaining 162 articles were subject to full text review and an additional 27 studies were added through examination of reference lists or reviews. 116 records were excluded for a number of reasons (see Fig. 1; flow chart). Forty-six articles were finally included for review. As described above, articles were split into separate 'studies' if there were multiple Phe-change conditions (e.g. increasing vs. decreasing Phe), or multiple participant groups were assessed. Overall, we considered 73 different studies, 37 of which reported cognitive outcomes, 22 well-being outcomes, and 14 neurophysiological outcomes and effects on neurological symptoms. We were particularly

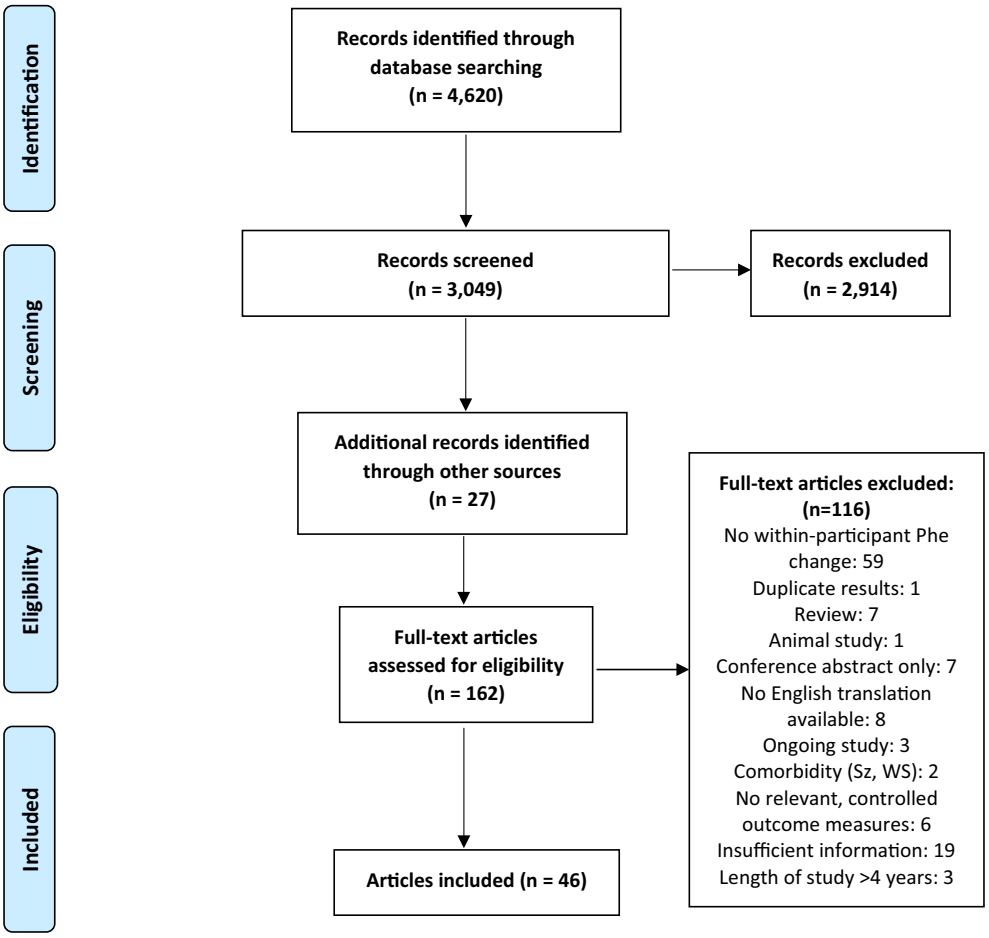

Fig. 1. Flowchart for systematic review of articles reporting cognitive, well-being, and/or neurophysiological outcomes of within-participant Phe-change; Sz = Schizophrenia, WS=West Syndrome.

interested in assessing results in adolescents/adult cohorts. We used a cut-off age of 15 years to split participants into child vs. adolescent/adult cohorts. This is based on the suggestion that diets start to be relaxed and Phe levels begin to rise in mid-late adolescence [10,32,103,105]. Studies including children (<15 years old), both alone and in combination with adults/adolescents, were grouped together under the heading 'mixed-age'.

2.1. Cognitive outcomes: results and discussion

We reviewed 37 studies reporting cognitive outcomes. Twenty-three were conducted with mixed-age cohorts (15 were children only) and 14 with adults/adolescents. Tables 1A and 2A in Appendix show parameters and outcomes in qualitative terms for individual studies ([1,5,6,11,15,17,19,28,30,31,33,36,39,40,43,44,50,59,66–68,76,78,84,87,90,91,100,104,108]). Both arithmetic and weighted averages across studies are reported.

Table 1A shows results for studies where Phe was decreased. This was mainly through diet resumption ($N = 11$) and, in a few cases, through Sapropterin or Pegvaliase treatment ($N = 2$ and 2). Most studies (11/15) involved early-treated participants only. Study-length varied widely, between 1 and 209 weeks (mean = 112, SD = 68). Panel A shows results for mixed-age studies ($N = 9$), and panel B for adult/adolescent studies ($N = 6$). Weighted Average Phe at baseline was **931** μmol/L for the mixed-age studies and **1246** μmol/L for the adult studies. After decrease, average Phe was **488** μmol/L for the mixed-age studies, and **562** μmol/L for the adult studies, with respective reductions in Phe of **387** μmol/L and **688** μmol/L. (arithmetic averages: 717 and 885). Overall, significantly more studies (13/15; 86.7%) showed a positive effect of decreasing Phe levels than showed no benefit ($\chi^2(1) = 8.1$, $p = .005$).

Table 2A shows results for studies where Phe was increased either through diet discontinuation ($N = 15$), or Phe loading ($N = 7$). Panel a) shows results for mixed-age studies ($N = 14$), panel b) for adult/adolescent studies ($N = 8$). Again, most studies (17/22) involved early-treated participants only. Study-length varied from 0.01 to 209 weeks (Mean = 101, SD = 89). Weighted average Phe at baseline was **543** μmol/L for the mixed-age studies and **763** μmol/L for the adult studies. Average Phe after increase was **1327** μmol/L for the mixed-age studies and **1535** μmol/L for the adult/adolescent studies with respective increases in Phe of **783** μmol/L and **772** μmol/L (arithmetic averages 918 and 710 μmol/L). Overall, most studies (14/22; 63.6%) showed a negative effect of increasing Phe levels (thus a positive effect of lower Phe levels), although this difference was not statistically significant ($\chi^2(1) = 1.6$, $p = .20$).

Considering all studies with cognitive outcomes, one can note that the higher Phe condition was well above levels recommended by both European and US guidelines, both in studies where Phe decreased and in those where it increased (but more so in the second case). Instead, lower Phe conditions for adult studies approached recommended levels at least according to European guidelines (**562** μmol/L and **763** μmol/L for studies decreasing and increasing Phe, when European guidelines recommend target levels of 600 μmol/L).

With few exceptions, differences in Phe across conditions were >**500** μmol/L. In studies showing a benefit with decreasing Phe, the smallest difference was **−208** μmol/L in a mixed cohort study [20] and

−668 μmol/L in an adult study [94]. Among studies where Phe was increased, the smallest difference in studies showing worse performance was **635** μmol/L among studies with children (reported by [51]) and **571** μmol/L among adult/adolescent studies (reported by [93]). This gives us a rough indication of the amount of difference in Phe that will result in a difference in cognitive outcomes.

Table 1 compares the number of studies showing vs. not showing a cognitive benefit when Phe is lower (using χ^2) and compares the respective parameters (Phe values, Phe-difference, length of study). Results are subdivided by age of cohort (here mixed-age studies were removed so that studies where participants were all <15 years old were compared with studies where participants were all ≥ 15 years old) and by direction of Phe change (increase vs. decrease). Statistical comparisons of parameters were carried out only when there were ≥5 studies in both the 'benefit' and 'no benefit' groups. However, we also report parameters for these subsets as they are informative on the range of values where cognitive effects were or were not demonstrated. We will do the same in the other tables showing results in the other domains.

When all studies were considered together, significantly more studies (and more participants) showed benefits than a null result (number

Table 1
Comparison of studies reporting a benefit vs. no benefit of lower Phe **on cognitive outcomes** in terms of their number (compared with χ^2), and treatment parameters (compared with univariate analysis of variance using either weighting or unweighted means, but keeping degree of freedom the same).'Phe difference' is the difference in Phe μmol/L achieved within studies.

	Cognitive studies ($N = 37$)						
	Studies showing benefit			Studies showing no benefit			χ^2/ t-test/GLM
Overall	Value	SD	Range	Value	SD	Range	*p* value
N studies	**27**	–	–	**10**	–	–	**0.005****
Sum participants	**758**	–	–	**134**	–	–	**<0.001****
Mean N participants	**28**	*45*	1–178	**13**	*7*	Apr-24	0.31
N studies with early treated ppts	**18**	–	–	**9**	–	–	0.08
Study length (weeks) - weighted	**104**	*78*	0.01–209	**54**	*89*	1–209	0.19
Study length (weeks) - arithmetic	**63**	*84*	0.01–209	**63**	*83*	1–209	0.99
Low Phe - weighted	**563**	*122*	121–993	**588**	*301*	284–1180	0.73
Low Phe - arithmetic	**562**	*197*	121–993	**626**	*288*	284–1180	0.46
High Phe - weighted	**1230**	*283*	618–2365	**1210**	*539*	470–2170	0.89
High Phe - arithmetic	**1448**	*400*	618–2365	**1206**	*481*	470–2170	0.13
Phe Difference - weighted	**691**	*303*	208–1751	**622**	*260*	186–990	0.58
Phe Difference - arithmetic	**916**	*431*	208–1751	**580**	*280*	186–990	**0.03***
Studies with Children (<15 years only)							
N studies	**11**	–	–	**4**	–	–	**0.05***
Study length (weeks) - weighted	**133**	*78*	1–209	**113**	99	1–209	
Study length (weeks) - arithmetic	**94**	*96*	1–209	**118**	*107*	1–209	
Low Phe - weighted	**556**	*180*	358–993	**407**	*125*	284–666	
Low Phe - arithmetic	**529**	*196*	358–993	**443**	*161*	284–666	
High Phe - weighted	**1378**	*367*	618–2365	**960**	*404*	470–1544	
High Phe - arithmetic	**1590**	*472*	618–2365	**1012**	*463*	470–1544	
Phe Difference - weighted	**823**	*317*	260–1751	**554**	*295*	186–878	
Phe Difference - arithmetic	**1061**	*470*	260–1751	**570**	*319*	186–878	
Studies with Adults (≥15 years only)							
N studies	**11**	–	–	**3**	–	–	**0.046***
Study length (weeks) - weighted	**89**	*62*	0.01–104	**14**	*29*	3–164	
Study length (weeks) - arithmetic	**33**	*54*	0.01–104	**37**	*58*	3–164	
Low Phe - weighted	**576**	*80*	121–863	**823**	*313*	536–1180	
Low Phe - arithmetic	**583**	*224*	121–863	**916**	*337*	536–1180	
High Phe - weighted	**1263**	*71*	1108–1600	**1653**	*408*	1337–2170	
High Phe - arithmetic	**1358**	*169*	1108–1600	**1618**	*478*	1337–2170	
Phe Difference - weighted	**690**	*72*	571–1443	**829**	*186*	315–990	
Phe Difference - arithmetic	**800**	*250*	571–1443	**702**	*348*	315–990	
Studies decreasing Phe							
N studies	**13**	–	–	**2**	–	–	**0.005****
Study length (weeks) - weighted	**97**	*74*	1–209	**20**	*8*	9–26	
Study length (weeks) - arithmetic	**47**	*72*	1–209	**18**	*12*	9–26	
Low Phe - weighted	**544**	*84*	121–761	**521**	*151*	409–713	
Low Phe - arithmetic	**498**	*196*	121–761	**561**	*215*	409–713	
High Phe - weighted	**1147**	*248*	618–2365	**901**	*334*	653–1327	
High Phe - arithmetic	**1301**	*447*	618–2365	**990**	*477*	653–1327	
Phe Reduction - weighted	**622**	*232*	208–1751	**380**	*183*	244–614	
Phe Reduction - arithmetic	**846**	*488*	208–1751	**429**	*262*	244–614	
Studies increasing Phe							
N studies	**14**	–	–	**8**	–	–	0.20
Study length (weeks) - weighted	**123**	*83*	1–209	**60**	*86*	0.01–209	0.13
Study length (weeks) - arithmetic	**75**	*92*	1–209	**75**	*90*	0.01–209	0.99
Low Phe - weighted	**604**	*168*	381–993	**599**	*287*	284–1180	0.97
Low Phe - arithmetic	**613**	*190*	381–993	**642**	*314*	284–1180	0.82
High Phe - weighted	**1450**	*230*	1200–2192	**1261**	*494*	470–2170	0.36
High Phe - arithmetic	**1584**	*306*	1200–2192	**1260**	*498*	470–2170	0.13
Phe Increase- weighted	**846**	*239*	571–1729	**662**	*268*	186–990	0.15
Phe Increase - arithmetic	**971**	*389*	571–1729	**618**	*288*	186–990	**0.03***

Note: values for Phe difference do not exactly match differences calculated from the table values because Phe post manipulation value was missed for one adult study decreasing Phe so difference could not be calculated. * significant at the 0.05 level, ** significant at the 0.01 level.

of studies showing a benefit over total number, 27/37 = 73%, $\chi^2(1) = 7.8$, $p = .005$). The same was true when children and adult/adolescent studies were considered separately (rate of studies showing a benefit: children: 73%; adults: 79%). When studies where Phe was decreased/increased were considered separately, 87% and 62% of studies, respectively, showed a benefit, with only studies where Phe was decreased reaching significance. Studies showing a benefit numerically lasted longer, although the difference was not significant. This was true for all sub-comparisons considering weighted means. Also, studies showing a benefit had numerically a larger difference in Phe (significant only with unweighted means). This was true numerically for all sub-comparisons except for the comparison involving adult/adolescent studies where studies showing no benefit appear to have a larger difference in Phe. However, there were only three studies in this group (see Table 2A panel B). They all involved an increase in Phe from baseline, but, perhaps notably, in 2/3 of these studies Phe, even at baseline, was well above what is recommended by current guidelines (1033 μmol/L and 1180 μmol/L compared with a recommendation of <600 μmol/L by European guidelines, [99]). This may indicate that negative effects of Phe do not increase linearly (i.e., the same difference in Phe does not have the same effect when Phe is higher overall). However, this is only speculative in the absence of more studies and corroborating evidence.

There was no difference in the proportion of studies showing a benefit when they involved children vs. adult/adolescents ($\chi^2 = 0.11$; $p = .74$). Equally, there was no difference in the parameters used by children and adult/adolescent studies showing a benefit both using unweighted means (study-length: t-test = −1.6; $p = .13$: Phe-difference t-test = 1.8; $p = .9$) and weighted means (study-length: F = 1.6; $p = .21$; Phe-difference: F = 2.0; $p = .17$). These results provide no evidence that the effects of Phe change at different ages, but one has to stress that they are null results, gathered post-hoc, and from otherwise very diverse studies.

Binary logistic regression predicting benefit/no benefit using the Phe difference was significant using unweighted means (β = −0.003; Wald 3.89; $p = .05$), but not with weighted means (because two large studies with average Phe differences dominate the results; β = −0.005; Wald 0.32; $p = .57$). When adding study length as a predictor the significance of Phe difference in an unweighted analysis reduces to 0.07 (β = −0.003; Wald 3.31; $p = .07$). Study length was not significant (β = 0.001; Wald 0.08; $p = .78$).

2.1.1. Meta-analyses

Twelve of the 37 cognitive studies provided quantitative outcomes across twenty different measures, allowing computation of effect sizes. A forest plot showing included studies, measures, and results is shown in Fig. 2. Table 3A (Appendix) outlines the parameters of all included studies. We calculated models using assumed pre-post correlations of 0.2, 0.5, and 0.8. Results were always similar. The results presented here and in Fig. 2 assume a correlation of 0.5. Overall, there was a positive and significant ES which tells us that cognition was better when Phe was lower. The pooled effect size, which captures the general effect of changing Phe, was 0.55, and clearly different from zero (95% confidence interval = 0.17–0.94, z = 2.8, p = .005).

We also ran separate analyses using age, Phe difference and study length as moderators. The best model had an interaction between *Study-length* and *Phe-difference* and a main effect of *Age*. Studies with larger Phe differences produced larger effects and this difference was clearest in longer studies (interaction: $G^2(1) = 13.4$, $p = .0002$). The best model was clearly better than a model that did not have any terms with Phe differences and included only *Study Length + Age*, showing the importance of Phe differences ($G^2(2) = 13.6$, $p = .001$). The main effect of *Age* was significant ($G^2(1) = 12.6$, $p = .0004$). The ES was also significant when adult/adolescent studies were considered on their own (ES = 0.57, z = 2.4, $p = .01$;).

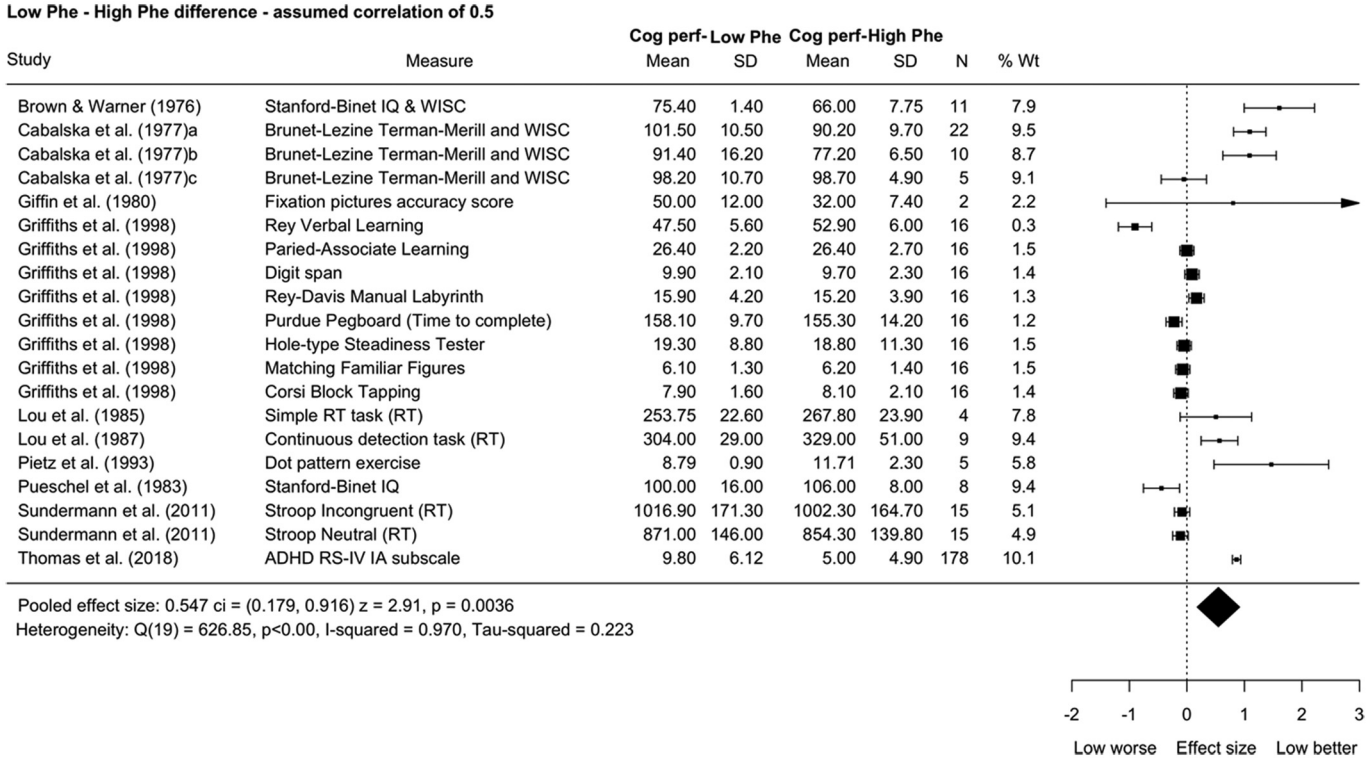

Fig. 2. Forest plot of studies included in the meta-analyses with an assumed correlation between studies of 0.5. Mean and SD for results on cognitive measures in low Phe and high Phe conditions are presented, along with number of participants (N) and study weightings (% Wt). Effect sizes for individual studies are indicated by the squares on the horizontal axis. Horizontal bars indicate 95% confidence intervals for each effect size. The black diamond indicates the overall point estimate and confidence interval across all studies.

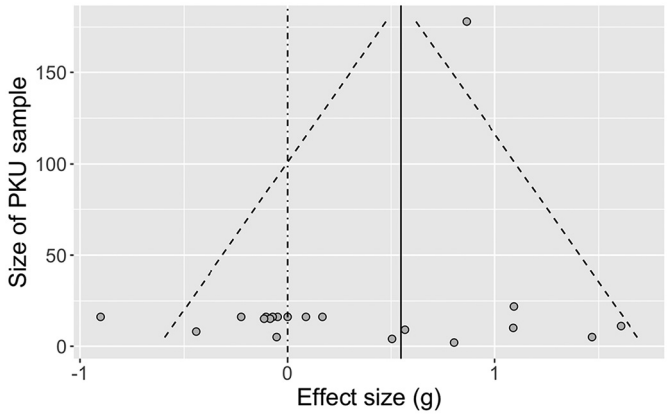

Fig. 3. Funnel plot of effect sizes as a function of sample size. The dash-dot vertical line marks the position of no benefit. The solid vertical line shows the overall effect size returned by the meta-analysis. The dashed diagonal lines are approximate 95% confidence limits around the overall effect size. These connect the confidence limit width from the study with the highest N to the confidence limits from the average of the 5 studies with the lowest N.

To check for bias due to studies with fewer participants we plotted a funnel plot (Fig. 3), that displays ES against sample size. Small N studies did not cluster on the right of the mean, which would be the hallmark of bias introduced by small N studies. An Egger's test, which uses number of participants as a moderator of effect size, was not significant ($z = 0.52$, $p = .61$), showing that participant numbers did not influence ES estimates. There was no evidence, therefore, that smaller studies with null/opposite effects had been excluded because of a publication bias, nor that the overall estimate of ES was biased by small N studies.

Finally, to check whether the overall effect size changed as studies with smaller N were added to the model, we ran a sensitivity analysis. The four largest studies were used for an initial estimate, and then studies were added in sets of 4. At each stage, a new cumulative estimate of effect size was calculated. Fig. 4 shows the results, assuming a correlation between 'pre' and 'post' conditions of 0.5. There was no indication that the estimate of the effect size was distorted by smaller studies and the overall estimate remained stable throughout.

2.2. Well-being: results and discussion

We reviewed 22 studies reporting well-being outcomes. Eight were conducted with mixed-age cohorts (5 of which were with children only) and 14 with adults/adolescents. Tables 4A and 5A in the Appendix show results when Phe was respectively decreased and increased. Both weighted and arithmetic means are reported.

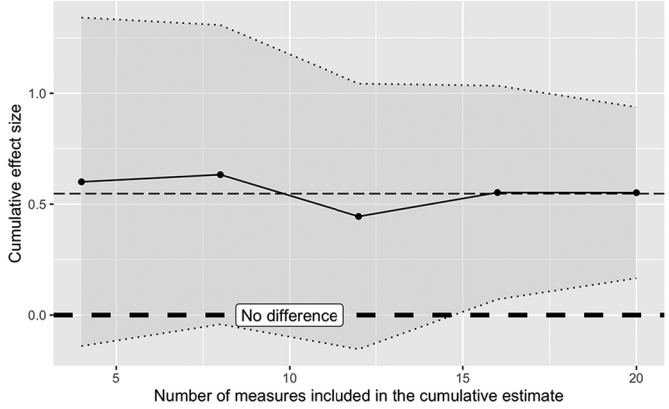

Fig. 4. Cumulative effect size estimates when studies with fewer participants are added across five bins.

Table 4A shows the results for studies where Phe was decreased. This was mainly through diet resumption ($N = 15$) and, in two cases, through Sapropterin or Pegvaliase treatment (N = 1 and 1). Most studies (12/17) involved late-treated participants. Study-length was between 8 and 209 weeks (mean = 109, SD = 58). Panel A shows results for mixed-age studies ($N = 5$), and panel B for adult studies ($N = 12$). Weighted average Phe at baseline was **1011** μmol/L for the mixed-age studies and **1365** μmol/L for the adult studies. After decrease, it was **619** μmol/L for the mixed-age studies and **588** μmol/L for the adult studies, with respective reductions in Phe of **406** μmol/L and **783** μmol/L.

Table 5A shows the results for studies where Phe was increased, either through diet discontinuation ($N = 4$) or Pegvaliase discontinuation (N = 1). Given the small number of studies, all age cohorts are presented together. 3/5 studies involved early-treated participants only. Study-length varied from 0.9 to 37 weeks (Mean = 11, SD = 12). Weighted average Phe at baseline was **536** μmol/L; Phe after increase was **1354** μmol/L, with an average increase of **818** μmol/L.

More studies (3/5; 60%) showed a negative effect of increasing Phe levels (thus a positive effect of lower Phe levels) although this is not significant given the small number of studies ($\chi^2(1) = 0.2$, $p = .66$). Notably, one study reported results in the opposite direction, with reduced emotional problems with diet relaxation. There were large variations in the size of Phe differences.

Considering the difference in Phe achieved by studies showing a benefit, the smallest difference in studies decreasing Phe was **−188** μmol/L in a mixed-age cohort [35] and **−297** μmol/L in adults [107]. In studies showing decrements with increasing Phe the smallest difference was **1611** μmol/L in children [64] and **571** μmol/L in adults [93].

Table 2 compares numbers and parameters of studies reporting better well-being with lower Phe with those reporting no benefit. For the age comparison, mixed-age studies were removed from analyses. When all studies were considered together, significantly more studies (and more participants) showed benefits than a null result (number of studies showing a benefit over total number 19/22 = 86%, $\chi^2(1) = 11.6$, $p = .001$). There were more studies showing benefits for all subcomparisons. However, because of small numbers, we only assessed separately the rate of studies showing benefits for adult/adolescent studies: 15/17 ; 88% ($\chi^2(1) = 9.9$, $p = .002$) and for studies decreasing Phe: 16/17; 94.1% ($\chi^2(1) = 13.2$, $p \leq 0.001$). Parameters could not be statistically compared because of the low number of studies showing no benefit. In numerical terms, there were no notable differences between high or low Phe levels or magnitude of Phe differences between studies with benefit vs. no benefit. Length of study, however, was much higher in studies reporting a benefit (Mean = 80, SD = 65) compared to those reporting no benefit (Mean = 14, SD = 12).

2.3. Neurophysiological outcomes: results and discussion

We reviewed 14 studies reporting neurophysiological outcomes after a Phe change. Ten were conducted with mixed-age cohorts (5 of which were with children only) and three with adults. Measures were obtained using MRI (N = 5), fMRI (N = 1), visual field examination (N = 1), EEG (N = 5), diffusion tensor imaging (DTI; $N = 2$) and automated fibre-tract quantification (AFQ; $N = 1$). We included Jaulent et al.'s [58] review as a single study, summarising parameters and outcomes for the eight new participants and 22 pre-existing case studies. This study considered neurological symptoms as well as MRI results. Tables 6A and 7A in the Appendix show results when Phe was respectively decreased and increased. Both weighted and arithmetic means are reported.

Table 6A shows parameters and effects for studies looking at effects of decreasing Phe through diet resumption ($N = 4$) and Sapropterin

Table 2
Comparison of studies reporting a benefit vs. no benefit of lower Phe **on well-being**, in terms of their number and treatment parameters. 'Phe difference' is the difference in Phe μmol/L achieved within studies.

	Well-being studies ($N = 22$)					
	Benefit			No benefit		
Overall	Value	SD	Range	Value	SD	Range
N studies	**19**	–	–	**3**	–	–
Sum participants	**451**	–	–	**36**	–	–
Mean N participants	**103**	*66*	1–178	**18**	*9*	5–24
N studies with early treated ppts	**7**	–	–	**1**	–	–
Length of study (weeks) - weighted	**107**	*59*	0.9–209	**14**	*12*	8–37
Length of study (weeks) - arithmetic	**46**	*50*	0.9–209	**18**	*17*	8–37
Low Phe - weighted	**595**	*67*	121–940	**490**	*67*	381–536
Low Phe - arithmetic	**611**	*183*	121–940	**447**	*80*	381–536
High Phe - weighted	**1290**	*348*	690–5448	**1343**	*390*	793–2143
High Phe - arithmetic	**1753**	*1161*	690–5448	**1424**	*679*	793–2143
Phe Difference - weighted	**758**	*354*	188–4722	**852**	*385*	412–1719
Phe Difference- arithmetic	**1234**	*1190*	188–4722	**977**	*671*	412–1719
Studies with Children (<15 years only)						
N studies	**4**	–	–	**1**	–	–
Length of study (weeks) - weighted	**199**	*45*	0.9–209	**37**	–	–
Length of study (weeks) - arithmetic	**61**	*100*	0.9–209	**37**		
Low Phe - weighted	**601**	*144*	*476–726*	**381**	–	–
Low Phe - arithmetic	**643**	*144*	*476–726*	**381**		
High Phe - weighted	**1153**	*630*	1027–5448	**793**	–	–
High Phe - arithmetic	**3155**	*1978*	1027–5448	**793**		
Phe Difference - weighted	**2819**	*1506*	1611–4722	**412**	–	–
Phe Difference- arithmetic	**3221**	*1558*	1611–4722	**412**		
Studies with Adults (≥15 years only)						
N studies	**15**	–	–	**2**	–	–
Length of study (weeks) - weighted	**88**	*33*	4–108	**8**	–	–
Length of study (weeks) - arithmetic	**42**	*28*	4–108	**8**	–	–
Low Phe - weighted	**593**	*59*	121–940	**517**	*43*	424–536
Low Phe - arithmetic	**589**	*209*	121–940	**480**	*79*	424–536
High Phe - weighted	**1349**	*205*	1105–1705	**1476**	*310*	1337–2143
High Phe - arithmetic	**1401**	*234*	1105–1705	**1740**	*570*	1337–2143
Phe Difference - weighted	**763**	*214*	297–1443	**959**	*353*	801–1719
Phe Difference- arithmetic	**839**	*375*	297–1443	**1260**	*650*	801–1719
Studies decreasing Phe						
N studies	**16**	–	–	**1**	–	–
Length of study (weeks) - weighted	**111**	*57*	11–209	**8**	–	–
Length of study (weeks) - arithmetic	**55**	*50*	11–209	**8**		
Low Phe - weighted	**594**	*67*	121–940	**424**	–	–
Low Phe - arithmetic	**609**	*196*	121–940	**424**		
High Phe - weighted	**1278**	*284*	690–4056	**2143**		
High Phe - arithmetic	**1520**	*759*	690–4056	**2143**		
Phe Reduction - weighted	**747**	*280*	188–3330	**1719**	–	–
Phe Reduction- arithmetic	**988**	*801*	188–3330	**1719**		
Studies increasing Phe						
N studies	**3**	–	–	**2**	–	–
Length of study (weeks) - weighted	**3**	*1*	0.9–4	**15**	*12*	8–37
Length of study (weeks) - arithmetic	**2**	*2*	0.9–4	**23**	*21*	8–37
Low Phe - weighted	**627**	*74*	476–726	**501**	*66*	381–536
Low Phe - arithmetic	**617**	*128*	476–726	**459**	*110*	381–536
High Phe - weighted	**1717**	*1222*	1220–5448	**1214**	*231*	793–1337
High Phe - arithmetic	**2918**	*2233*	1220–5448	**1065**	*385*	793–1337
Phe Increase - weighted	**1090**	*1212*	571–4722	**713**	*165*	412–801
Phe Increase arithmetic	**2301**	*2160*	571–4722	**606**	*275*	412–801

Note: values for Phe difference do not exactly match differences calculated from the table values because Phe post manipulation value was missed for one adult study and one child studies decreasing Phe so difference could not be calculated.
* significant at the 0.05 level, ** significant at the 0.01 level.

treatment ($N = 2$). Most studies (5/6) involved early-treated participants only. Study-length was between 26 and 126 weeks (mean = 39, SD = 15). Weighted Phe at baseline was **1240** μmol/L; after decrease it was **770** μmol/L, with an average reduction of **463** μmol/L.

Table 7A shows the results for studies where Phe was increased either through diet discontinuation ($N = 6$) or Phe loading (N = 2). All studies involved early-treated participants only. Study-length varied from 0.01 to 209 weeks (Mean = 103, SD = 99). Weighted average Phe at baseline was **668** μmol/L; after increase, it was **1442** μmol/L, with an average increase of **774** μmol/L. Overall, 4/8 (50%) of studies showed a negative effect of increasing Phe levels (thus a positive effect of lower Phe levels).

Among the studies which demonstrated a benefit, the smallest difference in Phe for studies decreasing Phe was **-244** μmol/L in a mixed age study [106]. In studies increasing Phe it was **435 μmol**/L in a child study ([22]; − Group C with mild PKU or Hyperphenylalanemia).

Table 3 compares the number of studies and the parameters of studies reporting better neurophysiological health with lower Phe levels with those reporting no benefit. For the age comparison, mixed-age studies were removed from analyses. Numerically, all comparisons showed more studies reporting a benefit. However, even considering all studies together, the difference did not reach significance: 64% ($\chi^2(1) = 1.1$, $p = .29$). The only marginal comparison was with studies decreasing Phe. 5/6 studies showed a benefit (83.3%; $\chi^2(1) = 2.7$, $p = .10$). Statistical comparisons of parameters were not carried out because of the low number of studies. At least numerically, studies reporting a benefit were longer, both when considered all together and in the individual sub-comparisons. Studies with a benefit did not show a larger difference in Phe (if anything, results were in the opposite direction).

3. General discussion

The current literature surrounding the effects of metabolic control on outcomes in PKU is strongly led by between-participant reports. These studies demonstrate the impact of Phe levels on cognition in children (see [23,27,49]) and in adolescents and adults [2,56,80,81].

Table 3
Comparison of studies reporting a benefit vs. no benefit of lower **Phe on neurophysiological outcomes**, in terms of their number and treatment parameters. 'Phe difference' is the difference in Phe μmol/L achieved within studies.

	Neurophysiological Studies ($N = 14$)						
	Benefit			No benefit			T-test / χ^2
Overall	Value	SD	Range	Value	SD	Range	p value
N studies	**9**	–	–	**5**	–	–	0.29
Sum participants	**105**	–	–	**50**	–	–	**<0.001****
Mean N participants	**17**	*7*	1–25	**15**	*6.3*	2–21	0.72
N studies with early treated ppts	**8**	–	–	**5**	–	–	0.41
Length of study (weeks) - weighted	**94**	*87*	0.01–209	**31**	*29*	0.01–104	0.19
Length of study (weeks) - arithmetic	**99**	*89*	0.01–209	**38**	*43*	0.01–104	0.18
Low Phe - weighted	**588**	*222*	300–969	**982**	*198*	476–1180	**0.01***
Low Phe - arithmetic	**490**	*196*	300–969	**871**	*290*	476–1180	**0.01***
High Phe - weighted	**1211**	*331*	653–1613	**1635**	*390*	1300–2170	0.09
High Phe - arithmetic	**1121**	*356*	653–1613	**1690**	*412*	1300–2170	**0.02***
Phe Difference - weighted	**620**	*214*	244–1000	**653**	*378*	300–1611	0.85
Phe Difference- arithmetic	**607**	*268*	244–1000	**819**	*544*	300–1611	0.36
Studies with Children (<15 years only)							
N studies	**3**	–	–	**2**	–	–	–
Length of study (weeks) - weighted	**209**	*0*	*209*	**42**	*22*	*1–52*	–
Length of study (weeks) - arithmetic	**209**	*0*	*209*	**27**	*36*	*1–52*	
Low Phe - weighted	**476**	*33*	400–509	**628**	*80*	476–666	–
Low Phe - arithmetic	**462**	*56*	400–509	**571**	*134*	476–666	
High Phe - weighted	**1244**	*167*	835–1362	**1653**	*229*	1544–2087	–
High Phe - arithmetic	**1160**	*284*	835–1362	**1816**	*384*	1544–2087	
Phe Difference - weighted	**768**	*135*	435–853	**1025**	*309*	878–1611	–
Phe Difference- arithmetic	**698**	*229*	435–853	**1245**	*518*	878–1611	
Studies with Adults (≥15 years only)							
N studies	**2**+	–	–	**2**	–	–	–
Length of study (weeks) - weighted	**55**	*15*	*52–126*	**22**	*44*	*0.01–104*	–
Length of study (weeks) - arithmetic	**89**	*52*	*52–126*	**52**	*74*	*0.01–104*	
Low Phe - weighted	**943**	*131*	300–969	**1149**	*62*	1033–1180	–
Low Phe - arithmetic	**635**	*473*	300–969	**1107**	*104*	1033–1180	
High Phe - weighted	**1613**	–	–	**1997**	*344*	1348–2170	–
High Phe - arithmetic	**1613**	–	–	**1759**	*581*	1348–2170	
Phe Difference - weighted	**644**	–	–	**848**	*283*	315–990	–
Phe Difference- arithmetic	**644**	–	–	**653**	*477*	315–990	
Studies decreasing Phe							
N studies	**5**	–	–	**1**	–	–	–
Length of study (weeks) - weighted	**42**	*17*	26–126	**33**	–	–	–
Length of study (weeks) - arithmetic	**53**	*42*	26–126	**33**			
Low Phe - weighted	**675**	*292*	300–969	**1000**	–	–	–
Low Phe - arithmetic	**491**	*271*	300–969	**1000**			
High Phe - weighted	**1214**	*454*	653–1613	**1300**	–	–	–
High Phe - arithmetic	**1090**	*489*	653–1613	**1300**			
Phe Decrease- weighted	**531**	*238*	244–1000	**300**	–	–	–
Phe Decrease- arithmetic	**552**	*346*	244–1000	**300**			
Studies increasing Phe							
N studies	**4**	–	–	**4**	–	–	–
Length of study (weeks) - weighted	**143**	*98*	0.01–209	**29**	*38*	0.01–104	–
Length of study (weeks) - arithmetic	**157**	*105*	0.01–209	**39**	*50*	0.01–104	
Low Phe - weighted	**506**	*53*	400–572	**969**	*261*	476–1180	–
Low Phe - arithmetic	**490**	*71*	400–572	**839**	*324*	476–1180	
High Phe - weighted	**1208**	*148*	835–1362	**1878**	*348*	1348–2170	–
High Phe - arithmetic	**1152**	*233*	835–1362	**1787**	*404*	1348–2170	
Phe Increase- weighted	**702**	*149*	435–853	**909**	*299*	315–1611	–
Phe Increase- arithmetic	**663**	*200*	435–853	**949**	*531*	315–1611	

Note: values for Phe difference do not exactly match differences calculated from the table values because Phe post manipulation value was missed for one adult study decreasing Phe so difference could not be calculated.* significant at the 0.05 level, ** significant at the 0.01 level.
+ = 2 studies reported a benefit of lower Phe levels in adult/adolescents, but only 1 provided details of Phe levels post Phe-change (reported in table).

However, they suffer from important limitations related to the fact that individuals with the best control may be those with better education and socio-economic status (variables which may also affect cognitive abilities) and with the best general health (which would affect brain health, mental well-being, and cognitive health). Studies with adults/adolescents are particularly problematic since metabolic control at these ages is strongly correlated with metabolic control at younger ages. Therefore, the correlations seen between current Phe and cognitive abilities, mental health, or brain measures may be due to collinearity with Phe levels during childhood. The strongest evidence to demonstrate an impact of Phe on outcomes, therefore, would come from within-participant studies, where outcomes are measured in the same participants at different times after the level of Phe has been altered. These studies are few, but a systematic review can allow us to collate results and reach firmer conclusions. In this paper, we reviewed studies investigating the effects of changes to Phe that take place within-participants, either through dietary changes or pharmacological interventions. We considered effects on cognitive, well-being, and neurophysiological measures. Where possible, we considered adult/adolescent studies, and studies with children or mixed-age cohorts separately. Because of difficulties in computing quantitative effects sizes, most of our analyses have involved a qualitative classification of studies showing vs. not showing a benefit when Phe levels were lower.

Our first, most important result was that, across domains, significantly more studies reported benefits of lower Phe than no benefit. This was true for cognition (27/37 = 73%), and well-being (19/22 = 86%), with a non-significant result in the same direction for neurophysiological/neurological outcomes (9/14 studies = 64%).

Cognitive benefits of lower Phe were reported in the domains of attention, executive function, and speed of processing, whilst more mixed outcomes were reported for general intelligence and working memory. A meta-analysis of 20 quantitative cognitive measures across 12 articles/publications demonstrated an overall estimated ES of 0.55, which was highly significant and indicates a sizeable effect. To illustrate what this means, this corresponds to a drop of 21 positions in a normally distributed population of 100 individuals from a starting position at the mean. These results support, and extend, reports from between-participant studies (for adults see [2,80]; for children see [54,57,83]).

In terms of mental well-being, benefits of lower Phe levels were reported on measures of anxiety, depression, aggression, and hyperactivity. The great majority of studies reported benefits. This is consistent with between-participant and correlational studies which have found that poor metabolic control is associated with more behavioural difficulties and personality problems in children and adults with PKU [20,52,56,60,88]. It is important to consider, however, that most assessments were carried out through questionnaires/self-report or observations. Our reviewed studies involved caregiver reports (e.g., by parents, teachers, clinicians; $N = 6$), self-report via questionnaire or interview ($N = 10$), and systematic observations ($N = 9$; note some studies used multiple methods). Among the observational studies, four relied on observations by nursing staff/key workers at residential institutions [41,45,53,62], one on observations by "trained inconspicuous observers" [71], one on observations made by teachers, parents, play-leaders, psychiatrists and/or nurses [64], and three did not specify how behavioural observations were made ([7]; Bickel et al. (1955) - conditions A & B; [34]). These measures are more subject to bias and expectation than quantitative, controlled, performance measures. Only three studies were carried out with measures taken under double-blind conditions. Of these, one reported some positive outcomes following diet initiation in late-treated AwPKU [62], one reported negative outcomes following Phe loading in early-treated AwPKU [93], and one reported no meaningful changes in a cohort of untreated adults [71]. Therefore, results on well-being should be interpreted with more caution. Not all between-participant studies have reported difficulties with well-being in AwPKU or correlations with Phe levels (e.g., [2,25,81]). In fact, some studies have highlighted that following a PKU diet can have not only positive, but also negative effects on well-being since the diet is unsociable and time-demanding (e.g., [12,75,77]).

Finally, neurophysiological/neurological benefits of lower Phe levels were reported in terms of reduced white matter abnormalities, increased diffusivity, reduced EEG abnormalities, improved motor responses, and reduced neurological symptoms (including upper limb tremors, brisk tendon reflexes, dysarthria, and blurred/loss of vision). This is consistent with findings from between-participant and correlational studies which have reported that white matter lesions and abnormalities in a number of brain areas are associated with elevated Phe levels [29,46,47,72,73,95].

A secondary aim of our review was to gather information on the metabolic parameters which elicited a change in outcomes. We had some indication that benefits were easier to demonstrate when differences in Phe between conditions were larger and when this difference was maintained for longer, but effects were not always consistent. With cognitive outcomes: 1. studies reporting a benefit of lower Phe (compared to no benefit) showed larger Phe differences between conditions, 2. Phe difference was a predictor of benefit/no-benefit in a binary logistic regression (but only with unweighted means) and 3. Phe difference predicted the size of effect in the meta-analysis. The same effects were not shown with well-being and neurophysiological studies, but this could be due to the small number of studies included in this comparison. We could only provide a rough estimate for the size of the Phe difference which elicited benefit. We can note that it was ≥ 600 μmol/L in all three domains. The average weighted difference was **691** μmol/L (SD = 278) for cognitive outcomes, **758** μmol/L (SD = 354) for well-being outcomes, and **620** μmol/L (SD = 214) for neurophysiological/neurological outcomes. Higher Phe levels for studies showing a benefit were also similar across domains: 1230 μmol/L (SD = 278), 1290 μmol/L (SD = 348) and 1211 μmol/L (SD =356) for cognitive, well-being and neurophysiological outcomes respectively, showing the negative impact of Phe above 1000 μmol/L

In terms of length of studies, across domains and sub-comparisons, studies demonstrating a benefit were numerically longer than studies showing no benefit (weighted average length in weeks, cognitive: 104 (SD = 78) vs. 54 (SD = 89); well-being: 107 (SD = 59) vs. 14 (SD = 12); neurophysiological: 94 (SD = 87) vs. 31 (SD = 29)). This was true for all sub-comparisons (except for studies looking at the effects of increasing Phe on well-being outcomes) although differences were either not statistically significant, or there were not enough results to assess significance.

These results give us an indication of the level of Phe difference that may be needed to demonstrate benefits. However, studies showed great variability and we really do not know whether smaller Phe reductions, or reductions occurring over a smaller time frame, would also show benefits. Positive differences have been reported in a few cases with Phe differences <400 μmol/L (cognition: [21], well-being: [12,35]). Some studies did compare performance across a span of only a few weeks, days, or hours, but they were very few (see for cognition: [54,61]; for well-being: [93]; for neurophysiology: [65]).

A final aim of our review was to assess outcomes separately for studies involving older PKU cohorts. Whilst the importance of maintaining low-Phe levels in childhood is undisputed, the importance of metabolic control in adulthood remains contested, with many adults and adolescents choosing to relax a strict diet after early adolescence [10,32,103,105]. Our results show that poor metabolic control, even in later life, can have a measureable negative impact. Studies with participants ≥ 15 years old demonstrated better cognition with lower Phe levels (11/14 = 79% of studies, with the great majority of studies involving early-treated participants) as well as better well-being (15/17 = 88% of studies). There were not enough studies focusing solely on older cohorts to assess effects on neurophysiological outcomes. Our meta-analysis, assessing the effect of changing Phe levels on cognition, demonstrated a substantial and significant ES (0.57) when studies with adolescents/adults were considered separately. There was no

indication that there were differences in the parameters used by adult/adolescent studies compared to child studies nor that adult/adolescent studies required a higher difference in Phe to show a benefit. There is too much variability between studies, however, to reach any firm conclusion. In adult/adolescent studies, cognition and well-being were detrimentally impacted when levels rose above above 1200 μmol/L. This does not mean, however, that lower levels are safe. There is a lack of studies with Phe levels in a lower range. Similarly, our results show that it is possible to undo some of damage caused by previously high levels of Phe by decreasing Phe. The extent of these reversals remains unclear, however, and it is unclear whether they can be achieved when Phe has remained elevated for extensive periods of time.

4. Limitations

A main limitation in our review is the low number of studies reporting outcomes in a quantitative way, such that they could be effectively accrued using meta-analysis. We had to limit most of our analyses to a qualitative and binary outcomes: whether or not the study showed benefits with lower Phe. Due to the paucity of within-participant studies in this field, we did not put a date limit on our literature search. The earliest studies included in this review were conducted in 1954, with a number of studies also conducted in the 60s and 70s. These studies often reported outcomes in qualitative terms, and studies reporting quantitative results often had only results in term of IQ. Results on a more comprehensive set of cognitive abilities would, therefore, be desirable. Studies assessing effects on well-being often included late-treated participants (14/22 = 64%) limiting their generalisability to early-treated participants that now constitute the great majority of the PKU population (although 7/8 with early treated participants did indicate a positive effect of lowering Phe). Moreover, well-being outcomes were generally not assessed blind to the dietary status of the participants. This may inflate positive results where behaviour and mood are more positively judged when Phe is lower, consistent with expectations. This is less of a concern for cognitive studies where outcomes are evaluated in terms of test performance. Lastly, only very few studies assessed neurophysiological changes in early-treated AwPKU after changes in Phe. These studies are important and hopefully more will be carried out in the future.

5. Conclusions

Our review showed significant benefits of lower Phe when Phe levels are changed within participants. There is some variability in the results reported by the literature, but the great majority of the reviewed studies reported benefits rather than null results and differences in numbers were highly statistically significant for cognitive and well-being outcomes. Results were also in the same direction, although not statistically significant, for neurophysiological outcomes. Moreover, meta-analyses comparing cognitive performance with lower vs. higher Phe showed a highly significant effect of moderate size (0.55). Importantly, the same results were obtained when cohorts of adults/adolescents were considered separately. These results add to consistent results from between-participant studies without having the same limitations. In between-participant studies, cognitive differences between groups with higher vs. lower Phe can potentially be due to differences in education, socio-economic status, and the underlying cognitive abilities of the participants and their families. These confounding influences are eliminated in studies where the same participants are assessed in conditions when Phe has changed.

Our conclusions are more limited in terms of the parameters necessary to see benefits (e.g., size of Phe difference, length of study). We only had some indication that the size of the Phe difference and the duration that new Phe levels are maintained affected outcomes (in particular cognitive outcomes). In the studies we reviewed, Phe changed substantially between low and high conditions (in general >500 μmol) and most of the studies had long durations, often spanning months. Thus we have no, or very limited, information about the effect of Phe changes which are smaller and/or are achieved and maintained within a smaller time span. Our review strongly highlights the need for studies that manipulate these parameters and evaluate effects, not only in IQ, but also in other, possibly more sensitive, tasks. This is important so that future intervention studies can provide a better understanding of the minimum metabolic changes that need to be achieved to see benefits. Our review also highlights the need for such studies to understand the lower time limit for a change in Phe to result in a meaningful change in outcomes.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2022.106969.

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