

Study	Main findings	Cohort characteristics					
		Number of patients	Age at baseline (years)	Follow-up time (months)	Blood Phe concentrations		
					Baseline (μmol/l)	Follow-up (μmol/l)	Change
	Neuro-imaging						
Christ 2013	Activation changed significantly in one out of 15 regions of interest.	12	23.6 ± 8.8	6	681	582	-15%
White 2013	Mean diffusivity improved in two out of 10 regions of interest.	12	18.2 ± 9.6	6	653	409	-37%
Clocks in 2021	White matter integrity improved significantly in 11 out of 14 tracts.	8	22.5 ± 10.1	6.4 ^a	693	375	-46%
	IQ						
White 2013	IQ did not significantly change after starting BH ₄ treatment, and was not significantly different compared to controls.	12	18.2 ± 9.6	6	653	409	-37%
	Executive functioning						
Christ 2013	Working memory significantly improved after starting BH ₄ treatment. Outcome was worse than controls at baseline, but there was no significant difference anymore after starting BH ₄ treatment.	12	23.6 ± 8.8	6	681	582	-18%
White 2013	Executive abilities did not significantly change after starting BH ₄ treatment, and were not significantly different compared to controls.	12	18.2 ± 9.6	6	653	409	-37%
Burton 2015	- In patients < 18 years, global executive functioning as well as one of the two subscales (metacognition index) was significantly better compared to controls. - In patients > 18 years, global executive functioning and neither of the two subscales were significantly different compared to controls - Improvement of global functioning was not significantly different compared to controls.	61 / 57 ^b	19.6 ± 10.1 / 20.2 ± 10.1 ^b	6 / 3 ^b	680 / 703	470 / 484	-31% / -31%
	Mental health						
Burton 2015	- Total ADHD score did not significantly differ compared to controls. However, one of the two subscales (inattention) was significantly better compared to controls. - In patients < 18 years, total ADHD score and one of the two subscales (inattention) were significantly better compared to controls. - In patients > 18 years, total ADHD score and neither of the two subscales were significantly better compared to controls. - Total ADHD score and the inattention subscale significantly decreased after starting BH ₄ treatment relative to the placebo group.	61 / 57 ^b	19.6 ± 10.1 / 20.2 ± 10.1 ^b	6 / 3 ^b	680 / 703	470 / 484	-31% / -31%

Table S9.1. Summary of outcomes in studies that investigated the effects of lower blood Phe concentrations following BH₄ treatment. Change in dietary Phe was not reported in these studies. ^aMean follow-up time (different follow-up times for different patients). ^bResults for two separate cohorts (BH₄ treatment for 26 weeks / BH₄ treatment for 13 weeks).