**Table H-1. Key outcomes of studies addressing Phe levels and executive function in individuals with PKU**

| **Azadi, 20091**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| Iran  Cross Sectional  **G1:** PKU subjects | **G1:** 10/10  Concurrent  PKU classification: : NR  **G1:** 13.3 ± 4.1 (6.6 – 19.8) | **Concurrent Phe (µmol/l):**  Patient1: 704  Patient 2: 1418  Patient 3: 1402  Patient 4: 1207  Patient 5: 2025  Patient 6: 1600  Patient 7: 704  Patient 8: 1487  Patient 9: 1400  Patient 10: 1691 | **Tower of London (TOL) - Average number of moves to complete:**  **2-move problems:**  **G1:** 2.3 ± 0.51  **3-move problems:**  **G1:** 4.12 ± 1.12  **4-move problems:**  **G1:** 8.85 ± 3.38  **5-move problems:**  **G1:** 10.47 ± 4.24  **TOL - Planning times (s):**  **2-move problems:**  **G1:** 7.14 ± 3.43  **3-move problems:**  **G1:** 10.84 ± 8.19  **4-move problems:**  **G1:** 9.45 ± 8.78  **5-move problems:**  **G1:** 8.38 ± 4.29  **TOL - Subsequent thinking times (s):**  **2-move problems:**  **G1:** 17.16 ± 8.03  **3-move problems:**  **G1:** 32.11 ± 19.66  **4-move problems:**  **G1:** 60.69 ± 27.46  **5-move problems:**  **G1:** 71.68 ± 31.18  **Continuous Performance Test (CPT):**  **Commission errors (number):**  **G1:** 5.50 ± 3.59  **Omission errors (number):**  **G1:** 4.80 ± 2.97  **Mean reaction time (s):**  **G1:** 0.79 ± 0.22  **Successfully recognized matches (number):**  **G1:** 67.7 ± 19.90  **Stroop single-task test:**  **Time in dots card (s):**  **G1:** 19.32 ± 7.79  **Errors in dots card (number):**  **G1:** 0.11 ± 0.33  **Time in word card (s):**  **G1:** 31.33 ± 18.45  **Errors in word card (number):**  **G1:** 0.11 ± 0.33  **Time in color card (s):**  **G1:** 41.77 ± 15.73  **Errors in color card (number):**  **G1:** 0.33 ± 0.70  **Difference index:**  **G1:** 22.78 ± 11.87 | **Spearman correlations:**  **Concurrent phe and:**  **TOL - Average number of moves to complete:**  **2-move problems:**  **G1:** 0.17  **3-move problems:**  **G1:** -0.14  **4-move problems:**  **G1:** 0.06  **5-move problems:**  **G1:** 0.23  **TOL - Planning times:**  **2-move problems:**  **G1:** -0.09  **3-move problems:**  **G1:** 0.08  **4-move problems:**  **G1:** 0.17  **5-move problems:**  **G1:** -0.01  **TOL -Subsequent thinking times:**  **2-move problems:**  **G1:** 0.07  **3-move problems:**  **G1:** 0.03  **4-move problems:**  **G1:** 0.3  **5-move problems:**  **G1:** 0.4  **Continuous Performance Test (CPT):**  **Commission errors (number):**  **G1:** 0.27  **Omission errors (number):**  **G1:** 0.15  **Mean reaction time:**  **G1:** -0.03  **Successfully recognized matches (number):**  **G1:** -0.15  **Stroop single test:**  **Time in dots card:**  **G1:** 0.02  **Errors in dots card (number):**  **G1:** 0.27  **Time in word card:**  **G1:** 0.03  **Errors in word card (number):**  **G1:** -0.27  **Time in color card:**  **G1:** 0.2  **Errors in color card (number):**  **G1:** 0.43  **Difference index:**  **G1:** 0.41 |

| **Sharman, 20092**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| Australia  Prospective Cohort  **G1:** PKU subjects | **G1:** 12/10  PKU classification: NR  Age (years): Baseline:  **G1:** 14.4 ± 2.08  Follow-up:  **G1:** 14.4 ± 2.16 | **Baseline (Jan. 2006) concurrent phe (µmols):**  601.30 ± 204.95 (270.00-970.00)  **Follow-up (Mar. 2006) concurrent phe (µmols):**  478.00 ± 274.26 (210.00-1100.00)  **Mean average phe age < 12 years (µmols):**  **G1:** 383.00 ± 96.91 (267.00-580.00)  **Mean average phe age > 12 years (µmols):**  **G1:** 491.75 ± 127.83 (367.00-742.00)  **Mean lifetime phe (µmols):**  **G1:** 395.80 ± 102.83 (276.00-626.00)  **Average phe in 2005:**  **G1:** NR | **BRIEF Inhibit Scale T-scores:**  **Baseline:**  **G1:** 54.30 ± 14.38  **Follow-up:**  **G1:** 58.40 ± 17.59 | **Phe level in 2005 and BRIEF Inhibit scale:**  **Baseline:**  **G1:** 0.671, p < 0.05  **Follow-up:**  **G1:** 0.752, p < 0.05  **Lifetime phe and BRIEF Inhibit scale:**  **Baseline:**  **G1:** 0.737, p < 0.01  **Baseline:**  **G1:** 0.883, p < 0.01 |

| **Moyle, 20073**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| Australia  Cross Sectional  **G1:** PKU patients | **G1:** 12/12  PKU classification: NR  Lifetime, Recent  Age (years) ± SE:  **G1:** 28.5 ± 3.3 | **Lifetime phe level:**  **G1:** NR  **Phe level obtained most recently before assessment:**  **G1:** NR | **Wechsler Adult Intelligence Scale-III (WAIS-III) mean scores ± SE:**  **Working Memory Index (WMI):**  **G1:** 103 ± 5.7  **Wechsler Memory Scale Third Edition (WMS-III) mean scores ± SE:**  **Working Memory (WM):**  **G1:** 104 ± 6.0  **Trail Making Test Part A (TMT-A):**  **G1:** 35 ± 4.8  **Trail Making Test Part B (TMT-B):**  **G1:** 75 ± 14.9 | **Lifetime phe with:**  **WAIS-III - Working Memory Index (WMI):**  **G1:** -.50  **WMS-III - Working Memory (WM):**  **G1:** -.51  **Trail Making Test Part A (TMT-A):**  **G1:** .20  **Trail Making Test Part B (TMT-B):**  **G1:** .54  **Phe level obtained most recently before assessment with:**  **WAIS-III - Working Memory Index (WMI):**  **G1:** -.24  **WMS-III - Working Memory (WM):**  **G1:** -.35  **Trail Making Test Part A (TMT-A):**  **G1:** .38  **Trail Making Test Part B (TMT-B):**  **G1:** .68\*, p < .05 |

\*Text in the Results section states “r(11) = -.68, p=.02.”

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| **Author/Year**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| Christ, 20064  USA  Prospective Cohort  **G1:** PKU subjects | **G1:** 26/26  Concurrent  PKU classification: NR  **G1:** 11.2 ± 3.1 years (6-18) | **Recent Phe (mg/dL):**  **G1:** 7.0 ± 5.6 (0.2-20.2) | **Go/no-go:**  **Reaction time (milliseconds):**  **Neutral:**  **G1:** 335 ± 60  **Inhibitory:**  **G1:** 443 ± 67  **Error rate (%):**  **Neutral:**  **G1:** 2.0 ± 2.0  **Inhibitory :**  **G1:** 31.7 ± 17.4  **Antisaccade:**  **Reaction time (msec):**  **Neutral:**  **G1:** 306 ± 61  **Inhibitory :**  **G1:** 392 ± 77  **Error rate (%):**  **Neutral:**  **G1:** 0.3 ± 0.7  **Inhibitory :**  **G1:** 12.1 ± 11.5  **Flanker:**  **Reaction time (msec):**  **Neutral:**  **G1:** 766 ± 212  **Inhibitory:**  **G1:** 777 ± 219  **Facilitatory:**  **G1:** 736 ± 195  **Error rate (%):**  **Neutral:**  **G1:** 5.8 ± 5.7  **Inhibitory :**  **G1:** 7.1 ± 8.9  **Facilitatory:**  **G1:** 4.6 ± 6.1  **Stroop:**  **Reaction time (msec):**  **Neutral:**  **G1:** 811 ± 173  **Inhibitory:**  **G1:** 875 ± 186  **Facilitatory:**  **G1:** 785 ± 164  **Error rate (%):**  **Neutral:**  **G1:** 1.1 ± 2.0  **Inhibitory:**  **G1:** 2.2 ± 3.2  **Facilitatory:**  **G1:** 0.6 ± 1.1 | **Correlation of Phe levels with Go/no-go, antisaccade, Flanker, and Stroop tests:** NR |

| **Wasserstein, 20065**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| USA  Cross Sectional  **G1:** PKU patients | **G1:** 10/10  Concurrent, lifetime  Classic  Age:  Mean NR  Age at test (years):  Patient 1 – 26  Patient 2 – 23  Patient 3 – 27  Patient 4 – 30  Patient 5 – 30  Patient 6 – 29  Patient 7 – 35  Patient 8 – 24  Patient 9 – 33  Patient 10 – 31 | **Concurrent Phe (mg/dl):**  Patient 1 – 17.1  Patient 2 – 17.6  Patient 3 – 17.5  Patient 4 – 25.8  Patient 5 – 19.2  Patient 6 – 6.8  Patient 7 – 18.1  Patient 8 – 22.0  Patient 9 – 26.4  Patient 10 – 19.0  **Phe level from birth to 12 years (mg/dl):**  Patient 1 – 6.2  Patient 2 – 5.6  Patient 3 – 6.3  Patient 4 – 6.5  Patient 5 – 9.6  Patient 6 – 8.5  Patient 7 – 9.5  Patient 8 – 7.7  Patient 9 – 4.7  Patient 10 – 7.6  **Phe level over 12 years** **(mg/dl):**  Patient 1 – 15  Patient 2 – 11.8  Patient 3 – 9.6  Patient 4 – 7.8  Patient 5 – 19.5  Patient 6 – 12.1  Patient 7 – 16.8  Patient 8 – NR  Patient 9 – 13.4  Patient 10 – 14.2 | **California Verbal Learning Test**  **Words remembered correctly:**  **G1:** 11.02, SD-NR  **Dependence on semantic clues:**  **G1:** 6.11, SD-NR | **Phe levels and CVLT test outcomes:** NR |

| **Gassio, 20056**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| Spain  Cross Sectional  **G1:** individuals with PKU  **G2:** individuals with hyper-phenyl-alanemia | **G1:** 37/37  **G2:** 35/35  Concurrent, Historical  **G1:** PKU classification: NR  **G2:**Hyperphenylalanemia  **G1:** 9.75 ± 5.25 years (2.7- 19.3)  **G2:** 7.8 ± 3.2 years (2.7-17.25) | **Phe from the day of study (µmol/l):**  **G1:** 388 ± 205 (123-1013)  **G2:** 237 ± 86 (98-413)  **Phe at diagnosis (µmol/l):**  **G1:** 1504 ± 739 (371-2802)  **G2:** 253 ± 106 (112-544)  **Index of Dietary Control** (IDC, average of medians of plasma phe obtained every 6 months)**, most recent 6-mo period:**  **G1:** 427 ± 191 (116-880)  **G2:** 231 ± 76 (106-359)  **IDC, first 6 yrs of life:**  **G1:** 354 ± 113 (182-656)  **G2:** NR  **IDC, 7 to 12 yrs of life:**  **G1:** 444 ± 145 (250-820)  **G2:** NR | **Wisconsin Card Sorting test, preservative errors:**  **G1:** 50 ± 11.2  **G2:** 48 ± 10.5  **Trail Making Test:**  **Trail A:**  **G1:** 43 ± 12.4  **G2:** 48 ± 14.1  **Trail B:**  **G1:** 44 ± 12.3  **G2:** 50 ± 10.1  **Conners' Continuous Performance Test (CPT):**  **Omissions:**  **G1:** 56 ± 11.5  **G2:** 56 ± 9.1  **Commissions:**  **G1:** 51 ± 10.3  **G2:** 48 ± 11.7  **Stroop:**  **Word reading:**  **G1:** 45 ± 8.0  **G2:** 50 ± 8.3  **Color naming:**  **G1:** 40 ± 8.9  **G2:** 48 ± 6.9  **Color word interference:**  **G1:** 42 ± 9.8  **G2:** 50 ± 6.6  **Resistance to interference:**  **G1:** 49 ± 6.4  **G2:** 51 ± 5.7 | **Phe day of study with Stroop color:**  **G1:** r=-0.457, p=0.019  **Phe day of study with Stroop color word interference:**  **G1:** r=-0.462, p=0.018  **IDC first 6 yrs of life with Stroop color-word interference:**  **G1:** r=-0.547, p=0.013  **IDC 7-12 yrs of life with Stroop Word reading:**  **G1:** r=-0.423, p=0.035  **IDC 7-12 yrs of life with Stroop color-word interference:**  **G1:** r=-0.413, p=0.04 |

| **Anderson, 20047, 8**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| Australia  Cross Sectional  **G1:** PKU participants  **G1a:** PKU participants with MRI  **G1b:** PKU participants with MRI and with no white matter abnormalities  **G1c:** PKU participants with MRI and mild white matter abnormalities  **G1d:** PKU participants with MRI and moderate white matter abnormalities  **G1e:** PKU participants with MRI and no white matter abnormalities- on strict dietary restrictions  **G1f:** PKU participants with MRI and mild white matter abnormalities-on strict dietary restrictions  **G1g:** PKU participants with MRI and moderate white matter abnormalities- on strict dietary restrictions | **G1:** 33  **G1a:** 32  **G1b:** 6  **G1c:** 12  **G1d:** 14  **G1e:** 5  **G1f:** 9  **G1g:** 5  Historical, Concurrent  Classic  **G1:** 11.18 ± 3.4  **G1a:** 11.2 ± 3.5  **G1b:** 9.1 ± 2 **G1c:** 9.8 ± 2.1  **G1d:** 13.2 ± 3.9  **G1e:** 8.3 ± 0.7  **G1f:** 8.9 ± 1.5  **G1g:** 9.2 ± 2.6 | **Concurrent phe (µmol/l) ± SD:**  **G1:** NR  **G1a:** NR  **G1b:** 400.3 ± 131.5  **G1c:** 435.3 ± 196.4  **G1d:** 786.2 ± 284.4  **Concurrent phe (µmol/l) ± SE:**  **G1e:** 362.20 ± 92.3  **G1f:** 372.00 ± 68.8  **G1g:** 665.20 ± 92.3  **Lifetime phe (average of yearly median) (µmol/l) ± SD:**  **G1:** NR  **G1a:** NR  **G1b:** 330.8 ± 42.2  **G1c:** 369.8 ± 46.2  **G1d:** 542.5 ± 132.7  **Lifetime phe (average of yearly median) (µmol/l) ± SE:**  **G1e:** 354.05 ± 35.3  **G1f:** 380.03 ± 26.3  **G1g:** 451.23 ± 35.3  **Early phe (first 6 months) (µmol/l) ± SE:**  **G1:** NR  **G1a-d:** NR  **G1e:** 356.00 ± 51.7  **G1f:** 401.33 ± 38.5  **G1g:** 396.00 ± 51.7  **Recent phe (previous 12 months) (µmol/l ± SE:**  **G1:** NR  **G1a-d:** NR  **G1e:** 383.00 ± 62.0  **G1f:** 352.67 ± 46.2  **G1g:** 592.00 ± 62.0 | **Neuropsychological Measures\*\*:**  **TEA-Ch-Sky Search ± SE:**  **G1:** 17.6 ± 0.5  **G1a:** NR  **G1b:** 17.9 ± 1.1  **G1c:** 18.5 ± 0.8  **G1d:** 16.5 ± 0.8  **TEA-Ch-Code Transmission ± SE:**  **G1:** 35.21 ± 0.8  **G1a:** NR  **G1b:** 37.7 ± 2  **G1c:** 34.7 ± 1.3  **G1d:** 34.6 ± 1.3  **TEA-Ch-Digital Distraction ± SE:**  **G1:** 3.56 ± 0.3  **G1a:** NR  **G1b:** 3.7 ± 0.7  **G1c:** 3.7 ± 0.4  **G1d:** 3.4 ± 0.3  **TEA-Ch-Sky Search Dual Task ± SE:**  **G1:** 125.12 ± 6.7  **G1a:** NR  **G1b:** 118.6 ± 17.2  **G1c:** 116.6 ± 11  **G1d:** 137.7 ± 11.2  **WISC III - Digit span – forwards ± SE:**  **G1:**  5.32 ± 0.2  **G1a-d:** NR  **WISC III - Digit span – backwards ± SE:**  **G1:** 3.27 ± 0.2  **G1a-d:** NR  **WAIS-III or WISC-III Digit Span ± SE:**  **G1:** NR  **G1a:** NR  **G1b:** 9 ± 1.3  **G1c:** 8.3 ± 0.9  **G1d:** 8.3 ± 0.9  **Tower of London (TOL) extra attempts ± SE:**  **G1:** 7.72 ± 0.7  **G1a:** NR  **G1b:** 5.8 ± 1.8  **G1c:** 7.9 ± 1.2  **G1d:** 8.5 ± 1.2  **Contingency Naming Test (CNT) - errors and self-corrections ± SE:**  **G1:** 23.50 ± 2.8  **G1a:** NR  **G1b:** 19.3 ± 7.2  **G1c:** 15.7 ± 4.6  **G1d:** 32.7 ± 4.6  \*\*Means for G1b, G1c, and G1d adjusted for age at testing and socioeconomic status. Means for G1 adjusted for age  **Cognitive Domains\*\*\*:**  **Attention** (TEA-Ch Sky Search, Code Transmission, Digital Distraction, and Dual Task) **± SE:**  **G1:** NR  **G1a:** NR  **G1b:** -0.02 ± 0.3  **G1c:** -0.12 ± 0.2  **G1d:** -0.60 ± 0.2  **G1e:** 0.49 ± 0.5  **G1f:** -0.74 ± 0.4  **G1g:** -1.46 ± 0.4  **Memory/Learning** (Digit span forwards and backwards, RAVLT and RVDLT trials 1 and totals) **± SE:**  **G1:** NR  **G1a:** NR  **G1b:** -0.23 ± 0.4  **G1c:** -0.27 ± 0.2  **G1d:** -0.56 ± 0.2  **G1e:** -0.48 ± 0.5  **G1f:** -0.66 ± 0.3  **G1g:** -1.12 ± 0.4  **Executive Function** (TOL extra attempts, RCF copy accuracy, CNT errors and self-corrections, and COWAT total words) **± SE:**  **G1:** NR  **G1a:** NR  **G1b:** -0.10 ± 0.4  **G1c:** -0.01 ± 0.2  **G1d:** -0.70 ± 0.2  **G1e:** -0.68 ± 0.3  **G1f:** -0.62 ± 0.2  **G1g:** -1.26 ± 0.3  \*\*\* Means adjusted for age, socioeconomic status and gender | **Lifetime Phe with:**  **Working memory (Digit span):**  **G1a:** R=-0.40, p=0.05  **Mental flexibility (CNT errors and self-corrections):**  **G1a:** R=0.55, p=0.005  **Early Phe (first 6 months) with:**  **Attention** (TEA-Ch Sky Search, Code Transmission, Digital Distraction, and Dual Task)**:**  **G1:** r=-.09  **Memory/Learning** (Digit span forwards and backwards, RAVLT and RVDLT trials 1 and totals)**:**  **G1:** r=-.22  **Executive Function:**  **G1:** r=-.08  **Recent Phe (previous 12 months) with:**  **Attention** (TEA-Ch Sky Search, Code Transmission, Digital Distraction, and Dual Task)**:**  **G1:** r=-.20  **Memory/Learning** (Digit span forwards and backwards, RAVLT and RVDLT trials 1 and totals)**:**  **G1:** r=-.22  **Executive Function** (TOL extra attempts, RCF copy accuracy, CNT errors and self-corrections, and COWAT total words)**:**  **G1:** r=-.37  **Concurrent Phe with:**  **Attention** (TEA-Ch Sky Search, Code Transmission, Digital Distraction, and Dual Task)**:**  **G1:** r=-.19  **Memory/Learning** (Digit span forwards and backwards, RAVLT and RVDLT trials 1 and totals)**:**  **G1:** r=-.29  **Executive Function** (TOL extra attempts, RCF copy accuracy, CNT errors and self-corrections, and COWAT total words)**:**  **G1:** r=-.19  **Lifetime Phe with:**  **Attention** (TEA-Ch Sky Search, Code Transmission, Digital Distraction, and Dual Task)**:**  **G1:** r=-.32  **Memory/Learning** (Digit span forwards and backwards, RAVLT and RVDLT trials 1 and totals)**:**  **G1:** r=-.49, p<.01  **Executive Function** (TOL extra attempts, RCF copy accuracy, CNT errors and self-corrections, and COWAT total words)**:**  **G1:** r=-.40 |

| **Channon, 20049-11**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| UK  Cross Sectional  **G1:** off-dietPKU subjects  **G2:** on-dietPKU subjects  **G3:** PKU subjects continuously treated | **G1:** 25  **G2:** 25  **G3:** 20  Lifetime, Recent, Concurrent  Classic, atypical  **G1:** 27.48 ± 4.55 (18-38)  **G2:** 26.68 ± 4.92 (18-33)  **G3:** 24.60 ± 4.62 (18-33) | **Mean Phe (µmol/l):**  **1-4 years of age:**  **G1:** 460.59 ± 181.91 (171.75-786.69)  **G2:** 450.58 ± 123.97(255.75-727.5)  **G3:** 418.13 ± 94.35 (255.75-596.67)  **5-8 years of age:**  **G1:** 586.5 ± 199.91 (276-986.25)  **G2:** 456.85 ± 127.3 (237.13-740)  **G3:** 430.64 ± 127.75 (225.00-680.00)  **9-12 years of age:**  **G1:** 917.69 ± 209.53 (430-1380)  **G2:** 697.3 ± 280.65 (175-1275)  **G3:** 715.34 ± 280.96 (175.00-1275.00)  **13-16 years of age:**  **G1:** 1153.24 ± 242.91 (859-1710)  **G2:** 775.7 ± 255.9 (422.25-1411.5)  **G3:** 790.72 ± 265.98 (453.38-1411.50)  **17-20 years of age:**  **G1:** 1345.79 ± 282.26 (845-2013)  **G2:** 867.73 ± 248.89 (448.00-1443.13)  **G3:** 891.88 ± 251.19 (448.00-1443.13)  **21-24 years of age:**  **G1:** 1362.55 ± 268.87 (850-1774.5)  **G2:** 850.74 ± 229.44 (323.75-1216.81)  **G3:** 818.46 ± 238.35 (323.75-1216.81)  **25-28 years of age:**  **G1:** 1408.19 ± 426.96 (989-2815.5)  **G2:** 868.63 ± 187.40 (572-1170.79)  **G3:** 878.94 ± 194.34 (493.56-1170.09)  **29-32 years of age:**  **G1:** 1320.46 ± 262.99 (995-1736)  **G2:** 795.75 ± 228.62 (470.32-1194.25)  **G3:** NR  **Concurrent Phe** **(µmol/l):**  **G1:** 1285.68 ± 197.83 (990-1651)  **G2:** 758.79 ± 261.27 (221.00-1233.00)  **G3:** 858.80 ± 285.28 (333.00-1432.00)  **Recent Phe (year preceding test) (µmol/l):**  **G1:** 1317.77 ± 221.78 (1013.67-1710)  **G2:** 797.62 ± 240.80 (283.40-1153.00)  **G3:** 788.90 ± 225.24 (338.09-1208.75) | **N-back percentage accuracy:**  **0-back:**  **G1:** 97.08 ± 2.46  **G2:** 98.83 ± 1.09  **G3:** NR  **1-back:**  **G1:** 95.65 ± 3.24  **G2:** 97.78 ± 1.53  **G3:** NR  **2-back:**  **G1:** 84.55 ± 7.62  **G2:** 88.93 ± 5.69  **G3:** NR  **N-back speed per item (s):**  **0-back:**  **G1:** 0.43 ± 0.05  **G2:** 0.45 ± 0.08  **G3:** NR  **1-back:**  **G1:** 0.60 ± 0.15  **G2:** 0.55 ± 0.13  **G3:** NR  **2-back:**  **G1:** 1.54 ± 1.17  **G2:** 1.34 ± 0.67  **G3:** NR  **Flanker percentage accuracy:**  **Compatible trials:**  **G1:** 98 ± 1.57  **G2:** 99.35 ± 1.03  **G3:** NR  **Incompatible trials:**  **G1:** 97.05 ± 2.28  **G2:** 97.65 ± 3.41  **G3:** NR  **Flanker speed per item (s):**  **Compatible trials:**  **G1:** 0.49 ± 0.07  **G2:** 0.45 ± 0.06  **G3:** NR  **Incompatible trials:**  **G1:** 0.52 ± 0.08  **G2:** 0.47 ± 0.05  **G3:** NR  **Attention:**  **Telephone search per minute:**  **G1:** NR  **G2:** NR  **G3:** 19.94 ± 4.82  **Telephone search and counting per minute:**  **G1:** NR  **G2:** NR  **G3:** 18.46 ± 4.88  **Self-ordered pointing:**  **6-word trials per minute:**  **G1:** NR  **G2:** NR  **G3:** 15.45 ± 4.17  **9-word trials per minute:**  **G1:** NR  **G2:** NR  **G3:** 12.90 ± 2.64  **12-word trials per minute:**  **G1:** NR  **G2:** NR  **G3:** 12.25 ± 2.70 | **N-back accuracy:**  **0-back with:**  **mean phe level age 1-4:**  **G1:** r=-0.19  **G2:** 0.29  **mean phe level age 5-8:**  **G1:** -0.05  **G2:** 0.23  **mean phe level age 9-12:**  **G1:** 0.16  **G2:** -0.41  **mean phe level age 13-16:**  **G1:** 0.15  **G2:** -0.17  **mean phe level age 17-20:**  **G1:** -0.09  **G2:** -0.15  **mean phe level age 21-24:**  **G1:** -0.11  **G2:** -0.26  **mean phe level age 25-28:**  **G1:** -0.10  **G2:** -0.36  **mean phe level age 29-32:**  **G1:** -0.29  **G2:** -0.56  **Concurrent phe level:**  **G1:** -0.07  **G2:** -0.33  **Recent phe level:**  **G1:** -0.08  **G2:** -0.38  **1-back with**:  **mean phe level age 1-4:**  **G1:** -0.12  **G2:** -0.47  **mean phe level age 5-8:**  **G1:** 0.04  **G2:** -0.48  **mean phe level age 9-12:**  **G1:** 0.44  **G2:** -0.01  **mean phe level age 13-16:**  **G1:** 0.21  **G2:** 0.13  **mean phe level age 17-20:**  **G1:** -0.15  **G2:** 0.18  **mean phe level age 21-24:**  **G1:** -0.54  **G2:** 0.02  **mean phe level age 25-28:**  **G1:** -0.12  **G2:** 0.20  **mean phe level age 29-32:**  **G1:** -0.25  **G2:** -0.04  **Concurrent phe level:**  **G1:** -0.24  **G2:** -0.14  **Recent phe level:**  **G1:** -0.19  **G2:** -0.07  **2-back with:**  **mean phe level age 1-4:**  **G1:** 0.13  **G2:** -0.21  **mean phe level age 5-8:**  **G1:** 0.02  **G2:** -0.11  **mean phe level age 9-12:**  **G1:** 0.24  **G2:** 0.21  **mean phe level age 13-16:**  **G1:** -0.17  **G2:** 0.39  **mean phe level age 17-20:**  **G1:** -0.24  **G2:** 0.34  **mean phe level age 21-24:**  **G1:** -0.26  **G2:** 0.22  **mean phe level age 25-28:**  **G1:** -0.49  **G2:** 0.59  **mean phe level age 29-32:**  **G1:** -0.22  **G2:** 0.32  **Concurrent phe level:**  **G1:** -0.24  **G2:** -0.07  **Recent phe level:**  **G1:** -0.19  **G2:** -0.08  **N-back speed:**  **0-back with:**  **mean phe level age 1-4**:  **G1:** -0.58, p<0.01  **G2:** 0.36  **mean phe level age 5-8:**  **G1:** -0.46  **G2:** 0.55, p<0.01  **mean phe level age 9-12:**  **G1:** 0.01  **G2:** 0.03  **mean phe level age 13-16:**  **G1:** -0.14  **G2:** 0.09  **mean phe level age 17-20:**  **G1:** -0.04  **G2:** 0.10  **mean phe level age 21-24:**  **G1:** 0.37  **G2:** 0.11  **mean phe level age 25-28:**  **G1:** 0.10  **G2:** -0.17  **mean phe level age 29-32:**  **G1:** 0.33  **G2:** -0.64  **Concurrent phe level:**  **G1:** 0.55, p<0.01  **G2:** 0.22  **Recent phe level:**  **G1:** 0.44  **G2:** -0.37  **1-back with:**  **mean phe level age 1-4:**  **G1:** -0.45  **G2:** -0.03  **mean phe level age 5-8:**  **G1:** -0.38  **G2:** 0.19  **mean phe level age 9-12:**  **G1:** -0.19  **G2:** 0.02  **mean phe level age 13-16:**  **G1:** -0.14  **G2:** 0.13  **mean phe level age 17-20:**  **G1:** 0.09  **G2:** 0.13  **mean phe level age 21-24:**  **G1:** 0.28  **G2:** 0.05  **mean phe level age 25-28:**  **G1:** 0.11  **G2:** -0.24  **mean phe level age 29-32:**  **G1:** 0.38  **G2:** -0.38  **Concurrent phe level:**  **G1:** 0.38  **G2:** 0.26  **Recent phe level:**  **G1:** 0.31  **G2:** 0.06  **2-back with:**  **mean phe level age 1-4:**  **G1:** -0.14  **G2:** -0.39  **mean phe level age 5-8:**  **G1:** -0.30  **G2:** -0.15  **mean phe level age 9-12:**  **G1:** 0.01  **G2:** 0.17  **mean phe level age 13-16:**  **G1:** -0.54, p<0.01  **G2:** 0.10  **mean phe level age 17-20:**  **G1:** -0.53  **G2:** -0.18  **mean phe level age 21-24**  **G1:** 0.07  **G2:** -0.30  **mean phe level age 25-28:**  **G1:** -0.43  **G2:** -0.01  **mean phe level age 29-32:**  **G1:** -0.11  **G2:** -0.29  **Concurrent phe level:**  **G1:** -0.06  **G2:** 0.23  **Recent phe level:**  **G1:** -0.14  **G2:** 0.08  **Flanker speed:**  **Compatible trials with:**  **mean phe level age 1-4:**  **G1:** -0.36  **G2:** 0.24  **mean phe level age 5-8:**  **G1:** -0.40  **G2:** 0.41  **mean phe level age 9-12:**  **G1:** -0.32  **G2:** -0.11  **mean phe level age 13-16:**  **G1:** -0.10  **G2:** 0.15  **mean phe level age 17-20:**  **G1:** -0.08  **G2:** 0.18  **mean phe level age 21-24**  **G1:** 0.35  **G2:** 0.22  **mean phe level age 25-28:**  **G1:** 0.26  **G2:** 0.17  **mean phe level age 29-32:**  **G1:** 0.43  **G2:** -0.59  **Concurrent phe level:**  **G1:** 0.44  **G2:** -0.18  **Recent phe level:**  **G1:** 0.41  **G2:** -0.20  **Flanker speed: Incompatible trials with:**  **mean phe level age 1-4:**  **G1:** -0.38  **G2:** 0.27  **mean phe level age 5-8:**  **G1:** -0.41  **G2:** 0.33  **mean phe level age 9-12:**  **G1:** -0.26  **G2:** -0.13  **mean phe level age 13-16:**  **G1:** -0.11  **G2:** 0.08  **mean phe level age 17-20:**  **G1:** -0.13  **G2:** 0.08  **mean phe level age 21-24**  **G1:** 0.28  **G2:** 0.19  **mean phe level age 25-28:**  **G1:** 0.26  **G2:** 0.03  **mean phe level age 29-32**:  **G1:** 0.25  **G2:** -0.63  **Concurrent phe level:**  **G1:** 0.38  **G2:** -0.24  **Recent phe level:**  **G1:** 0.32  **G2:**-0.21  **Correlations between N-back accuracy, N-back speed, and Flanker speed with phe levels for** **G3:** NR  **Attention (combined Telephone search and Telephone search with counting ) and:**  **mean phe level age 1-4:**  **G3:** .19  **mean phe level age 5-8:**  **G3:** .18  **mean phe level age 9-12:**  **G3:** .21  **mean phe level age 13-16:**  **G3:** -.06  **mean phe level age 17-20:**  **G3:** -.03  **mean phe level age 21-24:**  **G3:** -.18  **mean phe level age 25-28:**  **G3:** -.59, p<0.05  **Concurrent phe level:**  **G3:** -.16  **Recent phe level:**  **G3:** -.19  **Self-ordered pointing (combined levels) and**  **mean phe level age 1-4:**  **G3:** .03  **mean phe level age 5-8:**  **G3:** -.06  **mean phe level age 9-12:**  **G3:** -.01  **mean phe level age 13-16:**  **G3:** -.13  **mean phe level age 17-20:**  **G3:** .44  **mean phe level age 21-24:**  **G3:** -.63, p<.05  **mean phe level age 25-28:**  **G3:** -.77, p<.01  **Concurrent phe level:**  **G3:** -.49, p<.05  **Recent phe level:**  **G3:** -.67, p<.01  **Correlations between attention and self-ordered pointing for G1 and G2:** NR |

| **Antshel 200312, 13**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| United States  Cross Sectional  **G1:** participants with PKU | **G1:** 46  Current  PKU classification: NR  **G1:** 10.75 ± 2.1 years (8-14) | **Current Phe (mg/dl)**  **G1:** 8.1 ± 6.2 (0.9 – 22.8) | **California Verbal Learning Test –Children’s Version (CVLT-C) Semantic Cluster Ratio:**  **G1:** 39.9 ± 7.4  **CVLT-C Trial 5 Number Correct:**  **G1:** 40.3 ± 9.2  **Stroop Color and Word Test Interference trial:**  **G1:** 50.7 ± 8.3  **Stroop Word Reading T score:**  **G1:** 44.0 ± 9.9 | **Current Phe level with:**  **CVLT-C Semantic Cluster Ratio:**  **G1:** r = -.543, p<.001  **CVLT-C Trial 5 Number Correct:**  **G1:** r = -.291, p<.001  **Stroop Word Reading:**  **G1:** r = -.498, p<.001 |

| **Huijbregts 200214**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| Netherlands  Retro-spective case series  **G1:** PKU subjects  **G1a:** PKU subjects age <11  **G1b:** PKU subjects age ≥11  **G1c:** PKU subjects with concurrent phe≤360 µmol/l  **G1d:** PKU subjects with concurrent phe≤360 µmol/l age<11  **G1e:** PKU subjects with concurrent phe≤360 µmol/l age ≥11  **G1f:** PKU subjects concurrent phe>360 µmol/l  G1g: PKU subjects concurrent phe>360 µmol/l age<11  G1h: PKU subjects concurrent phe>360 µmol/l age≥11 | **G1:** 57  **G1a:** 27  **G1b:** 30  **G1c:** 22  **G1d:** 11  **G1e**:11  **G1f:** 35  **G1g:** 16  **G1h:** 19  Lifetime, Concurrent  Classical  **G1:** 11.0 ± 2.1  **G1a:** 9.1 ± 1.1  **G1b:** 12.7 ± 1.1  **G1c:** 11.2 ± 2.2  **G1d:** 9.4 ± 1.4  **G1e:** 12.9 ± 1.3  **G1f:** 10.9 ± 2.1  **G1g:** 8.9 ± 0.9  **G1h:** 12.6 ± 1.0 | **Concurrent phe (µmol/l):**  **G1:** 461 ± 259  **G1a:** 424 ± 218  **G1b:** 494 ± 291  **G1c:** 206 ± 99  **G1d:** 218 ± 77  **G1e:** 194 ± 119  **G1f:** 621 ± 190  **G1g:** 566 ± 161  **G1h:** 668 ± 203  **IDC (mean of all half-year median phe levels) (µmol/l):**  **G1:** 344 ± 115  **G1a:** 354 ± 150  **G1b:** 335 ± 75  **G1c:** 295 ± 67  **G1d:** 281 ± 64  **G1e:** 307 ± 70  **G1f:** 372 ± 128  **G1g:** 396 ± 169  **G1h:** 351 ± 75 | **ANT Mean RT sustained attention (ms):**  **G1d:** 1331, SD-NR  **G1e:** 1040, SD-NR  **G1g:** 1658, SD-NR  **G1h:** 1110, SD-NR  **Mean series time (MST); see following set of values for SD:**  **G1d:** 15.98  **G1e:** 12.48  **G1g:** 19.90  **G1h:** 13.32  **Standard deviation of Mean series time (a measure for the stability of performance (Fluctuation in Tempo)):**  **G1d:** 2.77  **G1e:** 1.98  **G1g:** 3.77  **G1h:** 2.24  **MST Corrected for Accuracy:**  **G1d:** 17.04, SD-NR  **G1e:** 13.23, SD-NR  **G1g:** 21.62, SD-NR  **G1h:** 14.15, SD-NR  **Mean number of false alarms 3 dots (FA3):**  **G1d:** 7.5, SD-NR  **G1e:** 5.6, SD-NR  **G1g:** 8.8, SD-NR  **G1h:** 4.8, SD-NR  **Mean number of Misses 4 dots (MISS):**  **G1d:** 20.1, SD-NR  **G1e:** 16.7, SD-NR  **G1g:** 28.4, SD-NR  **G1h:** 22.1, SD-NR  **Mean number of false alarms 5 dots (FA5):**  **G1d:** 10.7, SD-NR  **G1e:** 10.9, SD-NR  **G1g:** 13.0, SD-NR  **G1h:** 9.8, SD-NR  **Number of misses – number of false alarms (BIAS):**  **G1d:** 11.0, SD-NR  **G1e:** 8.5, SD-NR  **G1g:** 16.3, SD-NR  **G1h:** 13.2, SD-NR | **Tempo (Mean series time corrected for accuracy)** **with:**  **Phe between ages 5 and 7:**  r=0.36, p=0.004  **IDC:**  r=0.27, p=0.026  **Phe between ages 2.5 and 4:**  r=0.26, p=0.029  **Fluctuation in Tempo with:**  **Phe between ages 5 and 7:**  r=0.38, p=0.002  **IDC:**  r=0.28, p=0.021  **Phe between ages 2.5 and 4:**  r=0.24, p=0.045  **Bias with**  **Phe between ages 5 and 7:**  r=0.29, p=0.019  **IDC:**  r=0.29, p=0.018  **Concurrent phe:**  r=0.24 p=0.043  **Bias over time with:**  **phe level between ages 5 and 7:**  r=0.40, p=0.002  **phe level between ages 2.5 and 4:**  r=0.28, p=0.023  **IDC:**  r=0.35, p=0.007 |

| **Luciana 200115**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| United States  Cross Sectional  **G1:** PKU patients | **G1:** 18  Classic  Lifetime, Recent (within 6 months prior to cognitive assessment)  17.88 ± 2.74 years | **Recent phe (mg/dl):**  **G1:** 16.3 ± 6.8 (5.3-28.8)  **Phe averages for 0-2 years, 3-4 years, 5-8 years, 9-13 years and 14-15 years of life:**  **G1:** NR | **Spatial working memory:**  **Easy-item errors:**  **G1:** .71 ± 1.7  **Hard-item errors:**  **G1:** 21.6 ± 16.8  **Strategy score:**  **G1:** 32.6 ± 4.6  **Tower of London planning:**  **Minimum move solutions:**  **G1:**  7.8 ± 1.8  **Average moves to complete 3- move problems:**  **G1:** 3.2 ± .4  **Average moves to complete 4-move problems:**  **G1:** 5.7 ± 1.2  **Average moves to complete 5-move problems:**  **G1:** 7.3 ± 1.9  **Planning Times:**  **3- move problems:**  **G1:** 5911.9 ± 4383.0  **4-move problems:**  **G1:** 9535.7 ± 6772.7  **5-move problems:**  **G1:** 8895.0 ± 5755.9  **ID/ED set shifting:**  **Stage reached:**  **G1:** 8.1 ± 2.0  **ID errors:**  **G1:** 4.4 ± 7.9  **ID trials:**  **G1:** 10.5 ± 7.6  **ED errors:**  **G1:** 5.5 ± 7.9  **ED trials:**  **G1:** 13.3 ± 10.6  **Reversal errors:**  **G1:** 5.75 ± 2.8 | **Spatial Working Memory-  Strategy and:**  **Phe within past 6 months:**  **G1:** .71, p<.01  **Phe 0-2 years:**  **G1:** -.11  **Phe 3-4 years:**  **G1:** .38, p<.10  **Phe 5-8 years:**  **G1:** .23  **Phe 9-13 years:**  **G1:** .39, p<.10  **Phe 14-15 years:**  **G1:** .65, p<.05  **Spatial Working Memory-  Errors and**  **Phe within past 6 months:**  **G1:** .13  **Phe 0-2 years:**  **G1:** -.44, p<.10  **Phe 3-4 years:**  **G1:** .26  **Phe 5-8 years:**  **G1:** .18  **Phe 9-13 years:**  **G1:** .30  **Phe 14-15 years:**  **G1:** .15  **Set shifting-Stage and**  **Phe within past 6 months:**  **G1:** NR  **Phe 0-2 years:**  **G1:** .24  **Phe 3-4 years:**  **G1:** -.41, p<.10  **Phe 5-8 years:**  **G1:** -.49, p<.05  **Phe 9-13 years:**  **G1:** -.57, p<.05  **Phe 14-15 years:**  **G1:** .03  **Tower of London-Perfect solutions and**  **Phe within past 6 months:**  **G1:** -.30  **Phe 0-2 years:**  **G1:** .54, p<.05  **Phe 3-4 years:**  **G1:** -.05  **Phe 5-8 years:**  **G1:** -.09  **Phe 9-13 years:**  **G1:** -.30  **Phe 14-15 years:**  **G1:** .04 |

| **Griffiths 199816**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| UK  Retro-spective case series  **G1:** individuals with PKU | **G1:** 11  Concurrent, lifetime  Classic  Median Age (years):  **G1:** 8.83 (5.11-11.92) | **Phe level birth to age 5 years (µmol/l):**  **G1:** 342 ± 126  **Lifetime phe (µmol/l):**  **G1:** 341 ± 125 (224-600)  **Concurrent phe (µmol/l):**  **G1:** 388 ± 127 (193-562) | **One-back continuous performance test (CPT):**  **Overall mean hit rate out of 80:**  **G1:** 72.18 ± 7.17  **Overall mean false alarm frequency:**  **G1:** 8.36 ± 7.24  **Overall mean reaction time (milliseconds):**  **G1:** 499 ± 81  **Two-back continuous performance test (CPT):**  **Overall mean hit rate:**  **G1:** 64.55 ± 7.54  **Overall mean false alarm frequency:**  **G1:** 9.64 ± 5.89  **Overall mean reaction time (milliseconds):**  **G1:** 509 ± 72 | **Lifetime phe with any one-back measure or two-back measure:**  **G1:** NS  **Phe for first 5 years of life with any one-back measure or two-back measure:**  **G1:** NS  **Concurrent phe with any one-back measure or two-back measure:**  **G1:** NS |

| **Pietz 199817**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| Germany  Cross Sectional  **G1:** PKU subjects | **G1:** 57  Classic  Lifetime, Concurrent  23.6 ± 3.4 (17-33) | **Phe 0-adult (mean of all half-year medians) (µmol/l):**  **G1:** 676 ± 157 (388-994)  **Phe 0-12 (mean of all half-year medians for first 12 years) (µmol/l):**  **G1:** 424 ± 158 (206-806)  **Phe 12-adult (mean of all half-year medians from 12 years of age up to adulthood) (µmol/l):**  **G1:** 964 ± 194 (642-1424)  **Concurrent phe (µmol/l):**  **G1:** 1085 ± 303 (362-1733) | **Slow videotracking level (distance):**  **G1:** 17.2 ± 6.7  **Slow videotracking stability (distance):**  **G1:** 6.5 ± 3.0  **Fast videotracking level (distance):**  **G1:** 37.9 ± 15.2  **Fast videotracking stability (distance):**  **G1:** 16.6 ± 11.8 | **Phe after 12 years of age with videotracking performance:**  **G1:** r=-0.34, p<.05  **Concurrent phe with videotracking performance:**  **G1:** r=-0.37, p<.01 |

| **Stemerdink 199518**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| Netherlands  Prospective Cohort  **G1:** PKU patients | **G1:** 33  Classical  Lifetime  11.8 ± 2.9 years (7.3-16.8) | **Phe levels first 4 years (µmol/l):**  **G1:** 408, SD-NR (222-650)  **Phe levels 2 years preceding testing (µmol/l):**  **G1:** 374, SD-NR (125-701) | **Eriksen and Schultz task performance:**  **Response times:**  **G1:** NR  **Error percentages:**  **G1:** NR  **Memory Search Task:**  **Response times:**  **G1:** NR  **Error percentages:**  **G1:** NR | **Mean Phe for first 4 years and:**  **Eriksen and Schultz task performance:**  **Response times:**  **G1:** 0.33, p<0.05  **Error percentage:**  **G1:** -0.004  **Memory Search Task:**  **Response times:**  **G1:** 0.03  **Error percentage:**  **G1:** 0.12  **Mean Phe 2 years before testing and:**  **Eriksen and Schultz task performance:**  **Response times:**  **G1:** 0.33, p<0.05  **Error percentages:**  **G1:** -0.08  **Memory Search Task:**  **Response times:**  **G1:** 0.03  **Error percentage:**  **G1:** -0.07 |

| **Weglage 199519-21**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| Germany  Prospective Cohort  **G1:** PKU patients | **G1:** 20/20  Concurrent, lifetime  Classic  Age:  **G1:**  **Test time 1:**  10 years, 11 mos ± 1.3 years (8.9-13.1)  (reported as median and mean of 10 years, 11 mos ± 1.3 years in Weglage 1996 and mean of 10.11 ± 1.3 years in Weglage 1995)  **Test time 2:**  14 yrs, SD-NR | **Concurrent phe (µmol/l):**  **G1:**  **Test time 1:** 582 ± 372 (84-1710) (583 ± 377 (85-1709) in Weglage 1995 and 1996)  **Test time 2:** 744 ± 456 (66-1944)  **Lifetime phe (mean of yearly medians) (µmol/l):**  **G1:**  **Test time 1:** 474 ± 144 (282-810) (476 ± 144 (279-818) in Weglage 1995 and 1996)  **Test time 2:** 534 ± 174 (276-1014)  **Phe 6 months prior to test (mean of monthly medians) (µmol/l):**  **G1:**  **Test time 1:** 624 ± 328 (80-1563)  **Test time 2:** NR  **Mean of yearly medians between test times 1 and 2 (µmol/l):**  **G1:** 576 ± 174 (276-1014) | **Test-d-2 (percentile scores):**  **G1:**  **Number of items completed:**  **Test time 1:** 37.2 ± 26.2 (8.1-90.3)  **Test time 2:** 60.0 ± 25.8  **Errors:**  **Test time 1:** 57.0 ± 27.6 (15.9-93.3)  **Test time 2:** 81.2 ± 26.8  **Number of items completed - errors:**  **Test time 1:** 35.5 ± 26.6 (3.0-76.0)  **Test time 2:** 65.8 ± 34.9  **CWIT-Stroop tasks:**  **G1:**  **Reading of color words (sec):**  **Test time 1:** 48.2 ± 11.1 (SD=10.6 with a range of (31-81) in Weglage 1996; NR in Weglage 1995)  **Test time 2:** 41.1 ± 10.3  **Color naming (sec):**  **Test time 1:** 83.5 ± 16.7 (57-121)  **Test time 2:** 67.4 ± 11.2  **Interference task time (sec):**  **Test time 1:** 153.7 ± 45.9 (105-300)  **Test time 2:** 110.6 ± 24.2  **Interference task mistakes (number):**  **Test time 1:** 15.4 ± 14.2 (0-45)  **Test time 2:** 11.6 ± 11.7  **WISC-R (short term memory):**  **Test time 1:** 10.2 ± 2.2 (6-14)  **Test time 2:** NR | **Concurrent phe with Number of items completed:**  **Test time 1:** r=0.41, p<0.05 (r=-0.41, p<0.05 in Weglage 1996)  **Test time 2:** r=-2.42, p<0.05  **Errors:**  **Test time 1:** r=-0.38, p<0.05  **Test time 2:** r=-2.39, p<0.05  **Number of items completed - errors:**  **Test time 1:** r=-0.39, p<0.05 (reported as r=0.38, p<0.05 in Weglage 1995)  **Test time 2:** r=-2.40, p<0.05  **Lifetime phe with**  **Number of items completed:**  **Test time 1:** NS  **Test time 2:** NS  **Errors:**  **Test time 1:** NS  **Test time 2:** NS  **Number of items completed - errors:**  **Test time 1:** NS  **Test time 2:** NS  **Phe 6 months prior to test with**  **Number of items completed:**  **Test time 1:** NR  **Test time 2:** NR  **Errors:**  **Test time 1:** NR  **Test time 2:** NR  **Number of items completed - errors:**  **Test time 1:** r=-0.39, p<0.05  **Test time 2:** NR  **Concurrent phe and:**  **reading of color words:**  **Test time 1:** NS  **Test time 2:** NS  **Color naming:**  **Test time 1:** NS  **Test time 2:** NS  **Interference task time:**  **Test time 1:** r=0.39, p<0.05  **Test time 2:** NS  **Mistakes (number):**  **Test time 1:** r=0.38, p<0.05  **Test time 2:** NS  **Lifetime phe and:**  **reading of color words:**  **Test time 1:** NS  **Test time 2:** NS  **Color naming:**  **Test time 1:** NS  **Test time 2:** NS  **Interference task time:**  **Test time 1:** NS  **Test time 2:** NS  **Mistakes (number):**  **Test time 1:** NS  **Test time 2:** NS  **Correlation of differences in CWIT performances between test times 1 and 2 and mean phe during the 3-year interval:** NS  **Concurrent phe with**  **WISC-R (short term memory):**  **Test time 1:** NS  **Test time 2:** NR  **Lifetime phe with**  **WISC-R (short term memory):**  **Test time 1:** NS  **Test time 2:** NR |

| **Ris 199422, 23**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| USA  Prospective cohort  **G1:** PKU subjects  **G1a:** PKU subjects with unaffected siblings | **G1:** 25  **G1a:**10  Concurrent  Classic  **G1:** 22 years, SD-NR  **G1a:** NR | **Concurrent phe (mg/dl):**  **G1:** 22, SD-NR  **Individual Concurrent Phe (µmol/l):**  Subject 1: 993  Subject 2: 1102  Subject 3: 1665  Subject 4: 1968  Subject 5: 1380  Subject 6: 1538  Subject 7: 920  Subject 8: 1162  Subject 9: 1120  Subject 10: 1483  Subject 11: 1084  Subject 12: 1635  Subject 13: 1659  Subject 14: 1804  Subject 15: 503  Subject 16: 1399  Subject 17: 254  Subject 18: 1586  Subject 19: 2252  Subject 20: 1164  Subject 21: 1284  Subject 22: 1810  Subject 23: 1011  Subject 24: 1368  Subject 25: 938 | **WCST-Perseverative Responses (raw scores):**  **G1:** 21 ± 32  **G1a:** 22 ± 39  **Attention Diagnostic Method (seconds):**  **G1:** 461 ± 132  **G1a:** 439 ± 125  **Individual WCST-Perseverative Responses:**  Subject 1: NR  Subject 2: 5  Subject 3: 7  Subject 4: 123  Subject 5: 11  Subject 6: 28  Subject 7: 8  Subject 8: 13  Subject 9: 39  Subject 10: 5  Subject 11: 17  Subject 12: 14  Subject 13: 9  Subject 14: 22  Subject 15: 6  Subject 16: 12  Subject 17: 6  Subject 18: 4  Subject 19: 115  Subject 20: 4  Subject 21: 16  Subject 22: NR  Subject 23: 7  Subject 24: 18  Subject 25: 3 | **Concurrent phe with WCST-Perseverative Responses:**  **G1:** 0.59, p<0.01  **Concurrent phe with Attention Diagnostic Method:**  **G1:** 0.34, p<0.10 |

| **Schmidt 199424**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| Germany  Prospective Cohort  **G1:** PKU subjects  **G1a:** PKU subjects who completed tests and were able to keep their Phe-levels according to high-low-high study design | **G1:** 19/14  **G1a:**14/14  Concurrent  PKU classification: NR  Age:  **G1:** 20.5 years SD-NR (17-24)  **G1a:** NR | **Mean Phe level (mg/dl):**  Test time 1:  **G1:** 23.4, SD-NR (12-30)  **G1a:** 22.0 ± 5.7  Test time 2:  **G1:** NR  **G1a:** 10.5 ± 3.7  Test time 3:  **G1:** NR  **G1a:** 23.5 ± 6.1  **Individual phe at Test Time 1 (mg/dl):**  Patient 1: 19.1  Patient 2: 19.0\*  Patient 3: 25.4  Patient 4: 23.1\*  Patient 5: 15.0  Patient 6: 21.0  Patient 7: 26.7  Patient 8: 24.7  Patient 9: 25.4  Patient 10: 16.8  Patient 11: 16.3\*  Patient 12: 12.4\*  Patient 13: 18.7  Patient 14: 29.7  Patient 15: 25.3  Patient 16: 16.6  Patient 17: 12.0  Patient 18: 9.4\*  Patient 19: 32.2  **Individual phe at Test Time 2 (mg/dl):**  Patient 1: 11.0  Patient 2: 16.8\*  Patient 3: 16.1  Patient 4: 8.5\*  Patient 5: 7.4  Patient 6: 6.1  Patient 7: 16.8  Patient 8: 11.6  Patient 9: 10.9  Patient 10: 7.5  Patient 11: 13.7\*  Patient 12: 2.0\*  Patient 13: 4.6  Patient 14: 16.3  Patient 15: 10.4  Patient 16: 8.5  Patient 17: 7.0  Patient 18: 12.4\*  Patient 19: 12.0  **Individual phe at Test Time 3 (mg/dl):**  Patient 1: 16.1  Patient 2: NR\*  Patient 3: 23.0  Patient 4:18.7\*  Patient 5: 35.2  Patient 6: 25.2  Patient 7: 25.9  Patient 8: 17.4  Patient 9: 18.4  Patient 10: 20.0  Patient 11: 14.8\*  Patient 12: 6.5\*  Patient 13: 20.9  Patient 14: 20.0  Patient 15: 36.6  Patient 16: 18.9  Patient 17: 25.4  Patient 18: 14.3\*  Patient 19: 25.3  \*Data from patients 2, 4, 11, 12 and 18 not included in data analysis. | **Dot Pattern Exercise (DPE):**  **Mean RT of 50 series (level of performance) (s):**  **Test time 1:**  **G1a:** 10.1  **Test time 2:**  **G1a:** 8.09  **Test time 3:**  **G1a:** 9.32  **SD of 50 series times (ms) (stability of performance):**  **Test time 1:**  **G1a:** 1381  **Test time 2:**  **G1a:** 777  **Test time 3:**  **G1a:** 1356  **Number of Errors (sum of misses, false alarms 3 and false alarms 5 dots):**  **Test time 1:**  **G1a:** 51.9  **Test time 2:**  **G1a:** 36.8  **Test time 3:**  **G1a:** 43.0  **Percentage of Errors:**  **Test time 1:**  **G1a:** 8.7  **Test time 2:**  **G1a:** 6.1  **Test time 3:**  **G1a:** 7.2  DPE test outcomes for **G1:** NR | **Phe levels with DPE test outcomes:** NR |

| **de Sonneville 199025**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| Germany  Prospective Cohort  **G1:** PKU patients  **G1a:** PKU patients with median concurrent Phe >9.5 mg/dl  **G1b:** PKU patients with median concurrent Phe <9.5 mg/dl | **G1:** 32  **G1a:** NR  **G1b:** NR  PKU classification: NR  Lifetime, concurrent  **G1:** 8.7 years SD-NR  **G1a:** NR  **G1b:** NR | **Concurrent phe:**  **G1:** NR  **G1a:** NR  **G1b:** NR  **Lifetime phe:**  **G1:** NR  **G1a:** NR  **G1b:** NR | **Dot Pattern Exercise:**  **Mean times per series:**  **G1:** 19.8 ± 3.7  **G1a:** 22.5 ± 5.3  **G1b:** 17.0 ± 2.5  **Accuracy (%) for false alarms to 3-dot patterns:**  **G1:** 4.0, SD-NR  **G1a:** NR  **G1b:** NR  **Accuracy (%) for Miss:**  **G1:** 4.0, SD-NR  **G1a:** NR  **G1b:** NR  **Accuracy (%) for false alarms to 5-dot patterns:**  **G1:** 4.5, SD-NR  **G1a:** NR  **G1b:** NR  **Calculation exercise (CAE) performance:**  **Number of errors-simple additions:**  **G1:** 0.9, SD-NR  **Number of errors-complex additions:**  **G1**: 2.5, SD-NR | **Eight median phe levels (measured at 6-month intervals since birth) with highest correlations with:**  **DPE SD series:**  Median 18: r=.75, p=.01  Median 14: r=.65, p=.01  Median 17: r=.64, p=.01  Median 04: r=.55, p=.01  Median 15: r=.51, p=.02  Median 12: r=.48, p=.02  Concurrent: r=.47, p=.01  Median 16: r=.47, p=.02  **DPE mean time over series:**  Median 18: r=.58, p=.04  Median 14: r=.51, p=.02  Median 17: r=.48, p=.05  Median 16: r=.46, p=.03  Median 01: r=.46, p=.02  Median 04: r=.45, p=.02  Median 15: r=.45, p=.04  Concurrent: r=.37, p=.05  **Calculation exercises simple additions:**  Median 16: r=.46, p=.02  Median 18: r=.42, p=.12  Concurrent: r=.42, p=.02  Median 02: r=.34, p=.05  Median 01: r=.32, p=.07  Median 10: r=.31, p=.09  Median 05: r=.31, p=.09  Median 12: r=.27, p=.16  **Calculation Exercises complex additions:**  Concurrent: r=.45, p=.01  Median 15: r=.29, p=.15  Median 01: r=.27, p=.15  Median 18: r=.24, p=.40  Median 13: r=.24, p=.24  Median 02: r=.20, p=.27  Median 12: r=.16, p=.40  Median 06: r=.16, p=.38 |

| **Welsh 199026**  **Country**  **Study Design**  **Groups** | **N Enrollment/ Follow-up**  **Type of Phe Measure**  **Disease Type**  **Age** | **Phe level** | **Key Outcomes** | **Correlation** |
| --- | --- | --- | --- | --- |
| USA  Prospective cohort  **G1:** PKU subjects | **G1:** 11/11  Lifetime, Concurrent  PKU classification: NR  Mean age (years): 4.64, SD-NR (4.08-5.75)  Individual Age (years):  Subject 1: 4.25  Subject 2: 5.75  Subject 3: 4.08  Subject 4: 5.17  Subject 5: 4.50  Subject 6: 4.83  Subject 7: 4.50  Subject 8: 4.67  Subject 9: 4.42  Subject 10: 4.33  Subject 11: 4.50 | **Concurrent phe:**  **G1:**NR  Subject 1: 13.0  Subject 2: 8.4  Subject 3: 10.6  Subject 4: 9.9  Subject 5: 9.9  Subject 6: 4.9  Subject 7: 17.9  Subject 8: 9.5  Subject 9: 7.5  Subject 10: 10.9  Subject 11: 1.1  **Mean lifetime phe:**  **G1:** NR  Subject 1: 9.2  Subject 2: 9.9  Subject 3: 7.9  Subject 4: 10.5  Subject 5: 11.4  Subject 6: 10.3  Subject 7: 14.0  Subject 8: 7.3  Subject 9: 8.3  Subject 10: 7.4  Subject 11: 9.5  **Highest phe level during infancy, before diet initiation:**  **G1:** NR  Subject 1: 44.5  Subject 2: 45.3  Subject 3: 36.1  Subject 4: 31.9  Subject 5: 51.1  Subject 6: 31.9  Subject 7: 50.1  Subject 8: 20.0  Subject 9: NR  Subject 10: 19.1  Subject 11: 43.0 | **Tower of Hanoi:**  **G1:** 7.46 ± 7.74 | **Tower of Hanoi with:**  **Concurrent phe:**  **G1:** r=-.46,  **Mean phe:**  **G1:** r=-.06  **Infant phe:**  **G1:** r=-.46 |

\* All quantities expressed as **mean ± 1 SD (range)** unless otherwise noted.