**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** |
| --- | --- | --- | --- | --- |
| IranCross Sectional**G1:** PKU subjects  | **G1:** 10/10Concurrent PKU classification: : NR**G1:** 13.3 ± 4.1 (6.6 – 19.8) | **Concurrent Phe (µmol/l):**Patient1: 704Patient 2: 1418Patient 3: 1402Patient 4: 1207Patient 5: 2025Patient 6: 1600Patient 7: 704Patient 8: 1487Patient 9: 1400Patient 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** |
| --- | --- | --- | --- | --- |
| AustraliaProspective Cohort**G1:** PKU subjects | **G1:** 12/10 PKU classification: NR Age (years):Baseline:**G1:** 14.4 ± 2.08Follow-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** |
| --- | --- | --- | --- | --- |
| AustraliaCross Sectional**G1:** PKU patients | **G1:** 12/12 PKU classification: NRLifetime, RecentAge (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, 20064USAProspective Cohort**G1:** PKU subjects  | **G1:** 26/26Concurrent 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** |
| --- | --- | --- | --- | --- |
| USACross Sectional**G1:** PKU patients | **G1:** 10/10Concurrent, lifetimeClassicAge:Mean NR Age at test (years):Patient 1 – 26Patient 2 – 23Patient 3 – 27Patient 4 – 30Patient 5 – 30Patient 6 – 29Patient 7 – 35Patient 8 – 24Patient 9 – 33Patient 10 – 31 | **Concurrent Phe (mg/dl):**Patient 1 – 17.1Patient 2 – 17.6Patient 3 – 17.5Patient 4 – 25.8Patient 5 – 19.2Patient 6 – 6.8Patient 7 – 18.1Patient 8 – 22.0Patient 9 – 26.4Patient 10 – 19.0**Phe level from birth to 12 years (mg/dl):**Patient 1 – 6.2Patient 2 – 5.6Patient 3 – 6.3Patient 4 – 6.5Patient 5 – 9.6Patient 6 – 8.5Patient 7 – 9.5Patient 8 – 7.7Patient 9 – 4.7Patient 10 – 7.6**Phe level over 12 years** **(mg/dl):**Patient 1 – 15Patient 2 – 11.8Patient 3 – 9.6Patient 4 – 7.8Patient 5 – 19.5Patient 6 – 12.1Patient 7 – 16.8Patient 8 – NRPatient 9 – 13.4Patient 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** |
| --- | --- | --- | --- | --- |
| SpainCross Sectional**G1:** individuals with PKU**G2:** individuals with hyper-phenyl-alanemia | **G1:** 37/37**G2:** 35/35Concurrent, 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** |
| --- | --- | --- | --- | --- |
| AustraliaCross 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:** 5Historical, 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** |
| --- | --- | --- | --- | --- |
| UKCross Sectional**G1:** off-dietPKU subjects **G2:** on-dietPKU subjects**G3:** PKU subjects continuously treated | **G1:** 25**G2:** 25**G3:** 20Lifetime, Recent, ConcurrentClassic, 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:** 46Current 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** |
| --- | --- | --- | --- | --- |
| NetherlandsRetro-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/lG1g: PKU subjects concurrent phe>360 µmol/l age<11G1h: 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:** 19Lifetime, ConcurrentClassical**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 StatesCross Sectional**G1:** PKU patients  | **G1:** 18ClassicLifetime, 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** |
| --- | --- | --- | --- | --- |
| UKRetro-spective case series**G1:** individuals with PKU | **G1:** 11Concurrent, lifetimeClassicMedian 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** |
| --- | --- | --- | --- | --- |
| GermanyCross Sectional **G1:** PKU subjects | **G1:** 57ClassicLifetime, Concurrent23.6 ± 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** |
| --- | --- | --- | --- | --- |
| NetherlandsProspective Cohort**G1:** PKU patients  | **G1:** 33ClassicalLifetime11.8 ± 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** |
| --- | --- | --- | --- | --- |
| GermanyProspective Cohort **G1:** PKU patients | **G1:** 20/20Concurrent, lifetimeClassicAge: **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** |
| --- | --- | --- | --- | --- |
| USAProspective cohort **G1:** PKU subjects**G1a:** PKU subjects with unaffected siblings | **G1:** 25**G1a:**10ConcurrentClassic**G1:** 22 years, SD-NR**G1a:** NR | **Concurrent phe (mg/dl):****G1:** 22, SD-NR**Individual Concurrent Phe (µmol/l):**Subject 1: 993Subject 2: 1102Subject 3: 1665Subject 4: 1968Subject 5: 1380Subject 6: 1538Subject 7: 920Subject 8: 1162Subject 9: 1120Subject 10: 1483Subject 11: 1084Subject 12: 1635Subject 13: 1659Subject 14: 1804Subject 15: 503Subject 16: 1399Subject 17: 254Subject 18: 1586Subject 19: 2252Subject 20: 1164Subject 21: 1284Subject 22: 1810Subject 23: 1011Subject 24: 1368Subject 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: NRSubject 2: 5Subject 3: 7Subject 4: 123Subject 5: 11Subject 6: 28Subject 7: 8Subject 8: 13Subject 9: 39Subject 10: 5Subject 11: 17Subject 12: 14Subject 13: 9Subject 14: 22Subject 15: 6Subject 16: 12Subject 17: 6Subject 18: 4Subject 19: 115Subject 20: 4Subject 21: 16Subject 22: NRSubject 23: 7Subject 24: 18Subject 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** |
| --- | --- | --- | --- | --- |
| GermanyProspective 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:**14/14Concurrent PKU classification: NRAge:**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 ± 3.7Test time 3:**G1:** NR**G1a:** 23.5 ± 6.1**Individual phe at Test Time 1 (mg/dl):**Patient 1: 19.1Patient 2: 19.0\*Patient 3: 25.4Patient 4: 23.1\*Patient 5: 15.0Patient 6: 21.0Patient 7: 26.7Patient 8: 24.7Patient 9: 25.4Patient 10: 16.8Patient 11: 16.3\*Patient 12: 12.4\*Patient 13: 18.7Patient 14: 29.7Patient 15: 25.3Patient 16: 16.6Patient 17: 12.0Patient 18: 9.4\*Patient 19: 32.2**Individual phe at Test Time 2 (mg/dl):**Patient 1: 11.0Patient 2: 16.8\*Patient 3: 16.1Patient 4: 8.5\*Patient 5: 7.4Patient 6: 6.1Patient 7: 16.8Patient 8: 11.6Patient 9: 10.9Patient 10: 7.5Patient 11: 13.7\*Patient 12: 2.0\*Patient 13: 4.6Patient 14: 16.3Patient 15: 10.4Patient 16: 8.5Patient 17: 7.0Patient 18: 12.4\*Patient 19: 12.0**Individual phe at Test Time 3 (mg/dl):**Patient 1: 16.1Patient 2: NR\*Patient 3: 23.0Patient 4:18.7\*Patient 5: 35.2Patient 6: 25.2Patient 7: 25.9Patient 8: 17.4Patient 9: 18.4Patient 10: 20.0Patient 11: 14.8\*Patient 12: 6.5\*Patient 13: 20.9Patient 14: 20.0Patient 15: 36.6Patient 16: 18.9Patient 17: 25.4Patient 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:** 7.2DPE 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** |
| --- | --- | --- | --- | --- |
| GermanyProspective 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: NRLifetime, 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=.01Median 14: r=.65, p=.01Median 17: r=.64, p=.01Median 04: r=.55, p=.01Median 15: r=.51, p=.02Median 12: r=.48, p=.02Concurrent: r=.47, p=.01Median 16: r=.47, p=.02**DPE mean time over series:**Median 18: r=.58, p=.04Median 14: r=.51, p=.02Median 17: r=.48, p=.05Median 16: r=.46, p=.03Median 01: r=.46, p=.02Median 04: r=.45, p=.02Median 15: r=.45, p=.04Concurrent: r=.37, p=.05**Calculation exercises simple additions:**Median 16: r=.46, p=.02Median 18: r=.42, p=.12Concurrent: r=.42, p=.02Median 02: r=.34, p=.05Median 01: r=.32, p=.07Median 10: r=.31, p=.09Median 05: r=.31, p=.09Median 12: r=.27, p=.16**Calculation Exercises complex additions:**Concurrent: r=.45, p=.01Median 15: r=.29, p=.15Median 01: r=.27, p=.15Median 18: r=.24, p=.40Median 13: r=.24, p=.24Median 02: r=.20, p=.27Median 12: r=.16, p=.40Median 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** |
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| USAProspective cohort**G1:** PKU subjects | **G1:** 11/11Lifetime, Concurrent PKU classification: NRMean 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:**NRSubject 1: 13.0Subject 2: 8.4 Subject 3: 10.6 Subject 4: 9.9 Subject 5: 9.9Subject 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:** NRSubject 1: 9.2Subject 2: 9.9 Subject 3: 7.9 Subject 4: 10.5Subject 5: 11.4Subject 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:** NRSubject 1: 44.5Subject 2: 45.3Subject 3: 36.1 Subject 4: 31.9Subject 5: 51.1Subject 6: 31.9 Subject 7: 50.1 Subject 8: 20.0 Subject 9: NRSubject 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.