Outcome at Age 4 Years in Offspring of Women With Maternal Phenylketonuria

The Maternal PKU Collaborative Study

Susan E. Waisbren, PhD
William Hanley, MD
Harvey L. Levy, MD
Harvey Shifrin, MA
Elizabeth Allred, MA
Colleen Azen, PhD
Pi-Nian Chang, PhD
Sanja Cipcic-Schmidt, Dipl-Psych
Felix de la Cruz, MD
Ramona Hall, MS
Reuben Matalon, MD
Jo Nanson, PhD
Bobbye Rouse, MD
Fritz Trefz, MD
Richard Koch, MD

PHENYLKETONURIA (PKU) in women increases the risk to their offspring for adverse outcomes. In the offspring of untreated women with maternal PKU, there is a 92% risk for mental retardation, 73% risk for microcephaly, 40% risk for low birth weight, and 12% risk for congenital heart disease.\(^1\) The precise mechanism of fetal damage in maternal PKU is still unknown, although it is clear that the abnormal intrauterine environment harms the fetus.\(^2,3\) Treatment with a phenylalanine-restricted diet begun prior to pregnancy reduces these risks.\(^3,4\) However, the extent to which risks are reduced in late or inadequately treated pregnancies has not been clearly established.\(^5,7\)

Context Untreated maternal phenylketonuria (PKU) increases risk for developmental problems in offspring. The extent to which this risk is reduced by maternal dietary therapy at various stages of pregnancy is not known.

Objective To determine whether dietary treatment during pregnancy of women with PKU affects developmental outcomes of offspring.


Setting A total of 78 metabolic clinics and obstetrical offices in the United States, Canada, and Germany.

Participants A total of 253 children of women with PKU (n = 149), with untreated mild hyperphenylalaninemia (n = 33), or without known metabolic problems (comparison group; n = 71) were followed up to age 4 years.

Intervention Women with PKU were offered a low-phenylalanine diet prior to or during pregnancy with the aim of maintaining metabolic control (plasma phenylalanine \(\leq 10\) mg/dL [\(\leq 605\) µmol/L]). Women with mild hyperphenylalaninemia, who had plasma phenylalanine levels of no more than 10 mg/dL (605 µmol/L) on a normal diet, were not treated.

Main Outcome Measures Children’s scores on cognitive and behavioral assessments (McCarthy Scales of Children’s Abilities, Test of Language Development, Achenbach Child Behavior Checklist, Vineland Adaptive Behavior Scales, and Home Observation for Measurement of the Environment), compared by maternal metabolic status at 0 to 10 weeks’, 10 to 20 weeks’, and after 20 weeks’ gestation.

Results Scores on the McCarthy General Cognitive Index decreased as weeks to metabolic control increased (\(r = -0.58; P < .001\)). Offspring of women who had metabolic control prior to pregnancy had a mean (SD) score of 99 (13). Forty-seven percent of offspring whose mothers did not have metabolic control by 20 weeks’ gestation had a General Cognitive Index score 2 SDs below the norm. Overall, 30% of children born to mothers with PKU had social and behavioral problems.

Conclusions Our data suggest that delayed development in offspring of women with PKU is associated with lack of maternal metabolic control prior to or early in pregnancy. Treatment at any time during pregnancy may reduce the severity of delay.

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Author Affiliations: Children’s Hospital, Boston, Mass (Drs Waisbren and Levy and Ms Allred); Hospital for Sick Children, Toronto, Ontario (Dr Hanley); National Institute of Child Health and Human Development, Bethesda, Md (Dr Shifrin and Dr de la Cruz); Children’s Hospital, Los Angeles, Calif (Drs Azen and Koch and Ms Hall); Children’s Hospital, Minneapolis, Minn (Dr Chang); University of Tuebingen, Tuebingen, Germany (Ms Cipcic-Schmidt); University of Texas Medical Branch, Galveston (Drs Matalon and Rouse); Royal University Hospital, Saskatoon, Saskatchewan (Dr Nanson); and Children’s Hospital of Reutlingen, Reutlingen, Germany (Dr Trefz).

Corresponding Author and Reprints: Susan E. Waisbren, PhD, Genetic Service, Children’s Hospital, 300 Longwood Ave, IC-107, Boston, MA 02115 (e-mail: waisbren@al.tch.harvard.edu).

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METHODS

The Maternal PKU Collaborative Study

The Maternal PKU Collaborative Study, begun in 1984, prospectively evaluates the effects of dietary treatment during pregnancy. The Children's Hospital of Los Angeles serves as the coordinating center for data entry and analysis. Four regional contributing centers in the United States, 2 in Canada, and 1 in Germany are responsible for recruitment and data collection at 78 participating centers. The participating centers obtained institutional review board approval either by submitting a proposal to their research committees or by accepting approval from the contributing center hospital. The institutional review boards from each of the 4 contributing centers reviewed the protocols and procedures and approved separate informed consent forms. Previous articles have focused on nutritional and genetic characteristics of the mother and on offspring anomalies, birth measurements, neonatal neurological status, and preliminary results of developmental testing.

All women with PKU known to metabolic clinics in the United States, Canada, and Germany were tracked at the start of the study and enrolled at the time of pregnancy. Women with mild hyperphenylalaninemia (MHP) were also invited to participate. Women with PKU were offered a low-phenylalanine diet prior to or during pregnancy with the aim of maintaining metabolic control (plasma phenylalanine, ≤10 mg/dL [≤605 μmol/L]). The women with MHP had plasma phenylalanine levels of less than 10 mg/dL (605 μmol/L) on a normal diet and treatment was not recommended. Almost all pregnant women with PKU or MHP agreed to participate. Spouses of men with PKU, women who had a previous child with a metabolic disorder, and women working in the hospitals where the study took place were then recruited to participate in the nonhyperphenylalaninemic (non-HPA) comparison group.

The final study includes 572 pregnancies, of which 412 were completed. There were 75 spontaneous terminations, 79 elective terminations, 3 stillborns, and 3 ectopic pregnancies. There were 4 sets of twins. Eight children died of complications associated with maternal PKU. A standard protocol for treatment of maternal PKU was provided to each participating center. The protocol specified the monitoring of plasma phenylalanine levels and dietary intake on a weekly basis and visits to a metabolic center once per trimester. Indices of nutrition status (including weight gain and amino acid levels) were evaluated during each trimester. Ultrasound examinations were performed at 20, 28, and 34 gestational weeks. In addition, an obstetrician followed up each woman for regular prenatal care. Offspring were evaluated developmentally in the neonatal period and at 12 and 24 months (Bayley Scales of Infant Development). Thereafter, they were evaluated every 2 to 3 years, through age 10 years. Clinic attendance, adherence to medical recommendations, and cooperation with follow-up varied considerably.

Preschool Evaluations. At the time of this report, 368 children from the United States and Canada meeting the criteria for inclusion had reached their 4-year birthday. Two offspring diagnosed as having PKU and 2 offspring diagnosed as having MHP were excluded. The children from Germany were excluded because a different test battery was used. Of the 253 offspring receiving the preschool psychological test battery, 149 were born to mothers with PKU, 33 had mothers with untreated MHP, and 71 had mothers in the non-HPA comparison group.

The Psychological Assessment Battery. The battery of psychological tests administered is presented in Table 1. For the first 6 years (at ages 3 and 5 years), the McCarthy Scales of Children’s Abilities was the only test administered. The McCarthy Scales include a General Cognitive Index (GCI) and indices for verbal, perceptual-performance, quantitative, memory, and motor skills. Although now often replaced by other preschool tests, the McCarthy Scales of Children’s Abilities includes memory and motor development scales. The McCarthy Scales have been used for other longitudinal studies involving preschool children.

By the seventh year of the study, additional tests were administered, but were scheduled at age 4 years. While 253 children received the McCarthy Scales of Children’s Abilities, 183 received the full battery of tests. The evaluation obtained closest to age 4 years was used when more than 1 was performed.

The Test of Language Development—Primary provides a composite spoken language score, which includes scales for listening, speaking, semantics, syntax, and phonology.

The Achenbach Child Behavior Checklist includes 112 behavioral items

Table 1. Psychological Tests Administered for Preschool Assessments

<table>
<thead>
<tr>
<th>Test Battery</th>
<th>McCarthy Scales of Children’s Abilities</th>
<th>Test of Language Development</th>
<th>Achenbach Child Behavior checklist</th>
<th>Vineland Adaptive Behavior Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary scale*</td>
<td>General Cognitive Index, 100(14)</td>
<td>Spoken Language, 100(15)</td>
<td>Total Problems, &gt;60</td>
<td>Composite Adaptive Behavior, 100(15)</td>
</tr>
<tr>
<td>Age range of normative sample, mo</td>
<td>36-83</td>
<td>48-83</td>
<td>48-83</td>
<td>42-83</td>
</tr>
<tr>
<td>Mean (SD) age, mo</td>
<td>50.0 (7.7)</td>
<td>60.2 (13.5)</td>
<td>57.0 (9.1)</td>
<td>54.6 (8.1)</td>
</tr>
<tr>
<td>No. of subjects who received test</td>
<td>253</td>
<td>232</td>
<td>192</td>
<td>200</td>
</tr>
<tr>
<td>No. (%) of subjects ≥ 1 SD below mean</td>
<td>101 (40)</td>
<td>80 (34)</td>
<td>28 (15)</td>
<td>77 (39)</td>
</tr>
</tbody>
</table>

*Values are expressed as mean (SD) except for the Achenbach Child Behavior Checklist, which is reflected as a cutoff T score.
that are rated by the parent or primary caregiver. T scores for total problems, internalizing behaviors, and externalizing behaviors are calculated. A cut-off score of 60 serves as the bottom of the clinical range for categorical discrimination between deviant and non-deviant groups. T scores for 9 behavioral subscales are also available. Scores above 67 indicate the clinical range.19

The Vineland Adaptive Behavior Scales are completed through a parent or caregiver interview. Standard scores are available for an adaptive behavior composite standard score and 4 domains: communication, daily living skills, socialization, and motor skills.20

The Home Observation for Measurement of the Environment (HOME) scale provides a measure of the physical circumstances of the home, variety of experiences offered to the child, and the richness of language used. It provides a total environmental stimulation score derived from the sum of items checked.21 When the evaluation was performed outside of the home, the inventory was administered through an interview format. Scores less than 85% were considered low.

The Wechsler Adult Intelligence Scale—Revised22 was used as the measure of maternal IQ and was administered to all women who had not been administered this test within 5 years of the start of the study.

Procedures
The majority of evaluations were conducted in the homes of the participants. The psychologists were not informed about maternal metabolic control during pregnancy or maternal IQ results. Standard test administration procedures were followed. Informed consent was obtained at the time of enrollment. All completed test protocols were sent without names to the psychology coordinating center in Boston, Mass, where results were recorded and checked for accuracy. They were then submitted to the coordinating center in Los Angeles, Calif, where the data were entered.

Data Analyses
Timing of maternal metabolic control was defined as the number of weeks of gestation that elapsed before plasma phenylalanine levels remained lower than 10 mg/dL (605 µmol/L). The maternal PKU offspring were categorized into 4 treatment groups related to timing of maternal metabolic control: (1) prior to pregnancy, (2) more than 0 up to 10 weeks; (3) more than 10 up to 20 weeks; and (4) more than 20 weeks or never in control. Results of cognitive and behavioral assessments in HPA and untreated MHP offspring were compared with results in the offspring from women in the non-HPA comparison group. Since timing of maternal metabolic control and other maternal factors were taken into account in multivariate analyses, each offspring was considered a case. Thirty-nine mothers had more than 1 child in the study. The distribution of test scores permitted use of parametric procedures. Statistical power was calculated at more than 80% for comparisons of each subgroup with the non-HPA comparison group if differences of 10 points were found on the standardized psychological tests, but not large enough to detect differences of 5 or fewer points in the untreated MHP and prior to pregnancy groups. Factor analysis was performed to confirm domains of strengths and weaknesses in the children (details available from the authors on request). The relationship between maternal metabolic control and offspring outcome (risk for a low GCI score) was determined through the use of logistic regressions. Variables that were potential confounders of the relationship between in utero exposure to phenylalanine and offspring GCI scores also were entered in the initial model. These included maternal IQ, assigned maternal plasma phenylalanine level (plasma phenylalanine level when on an unrestricted diet), maternal age, socioeconomic status,23 and level of stimulation provided to the child in the home. The model was reduced, with variables being dropped 1 at a time, until remaining variables reached P<.30. For treated HPA pregnancies, the effect of birth order was tested through paired t tests. Also, for the treated HPA pregnancies, results from the 2-year evaluation were compared with results from the preschool evaluation at age 4 years using paired t tests. Statistical programs from Systat24 and Stata25 were used. P<.05 was used as the criterion for significance.

RESULTS
Maternal Characteristics
A total of 205 women enrolled in the Maternal PKU Collaborative Study gave birth to 253 offspring who received evaluations at age 4 years. As noted in TABLE 2, the majority of women with PKU attained metabolic control after 10 gestational weeks. Maternal IQ was lower in these women and their assigned plasma phenylalanine level was higher. Their education and level of social position were lower.

Preschool evaluations were not obtained for 115 children, usually because their mothers could not be located or did not respond to repeated telephone calls and letters. Missing cases were almost evenly distributed among the study groups (χ^2 = 9.3; P = .10). Using t tests, no significant differences were found between mothers whose children received the preschool evaluation and mothers of children for whom these data were missing in terms of the following variables: maternal IQ (t_{303} = 0.91; P = .36), assigned plasma phenylalanine level (t_{302} = 0.91; P = .36), or socioeconomic position (P = .80). Children whose mothers were younger (t_{370} = 2.4; P = .01) and whose average plasma phenylalanine levels were higher during pregnancy (t_{306} = 2.1; P = .04) were less likely to have been evaluated.

Effects in Offspring
Cognitive. Results from the McCarthy Scales of Children’s Abilities are presented in TABLE 3. The GCI and subscale scores on the McCarthy Scales declined as the number of weeks to metabolic control increased. A clear linear relationship between number of weeks gestation until maternal meta-
bolic control and the McCarthy GCI score suggests a dose-response association (r = −0.58; P < .001). The percentage of children attaining scores 1 and 2 SDs below the mean increased as metabolic control decreased. Scores on each of the McCarthy subscales followed a similar pattern.

A group of 10 children had mothers who attained metabolic control after pregnancy began but within 6 weeks of gestation. They had a mean (SD) GCI score of 96 (15). Overall, they performed not as well as those treated prior to conception (mean [SD] GCI score, 99 [13]). Two performed more than 1 SD below the normative mean (GCI # 86). None of these children performed in the range of mental retardation (GCI ≤ 72), while 8 of 16 offspring whose mothers attained metabolic control between 6 and 10 weeks’ gestation had a GCI score of 86 or less, with 3 of them having a score of 72 or less.

In analyses describing the developmental profile in maternal PKU, children from the untreated MHP and treated pregnancies were grouped since they shared patterns of high and low scores. Factor analysis of data from the combined HPA groups confirmed 3 factors: verbal/memory (varimax rotation factor loadings .0.75), perceptual performance/motor score (factor loadings .0.67), and quantitative (factor loadings .0.60). In all HPA groups, there was a consistent pattern of weaknesses in language/memory and quantitative domains on the McCarthy Scales. The verbal score was significantly lower than the perceptual performance score (t181 = −4.9; P < .001) and the motor score (t181 = −3.2; P = .002), but was not significantly different from the quantitative score (t181 = 0.82; P = .41) or the memory score (t181 = 0.42; P = .67). The results of the Test of Language Development suggest specific effects in expressive language and memory. Scores were 1 SD or more below the mean for 79% of the children on sentence imitation, 70% on word discrimination, 86% on grammar use, and 53% on articulation. The children perfor-

### Table 2. Maternal Characteristics of Children Receiving a Preschool Evaluation Compared With Children Whose Preschool Evaluation Is Missing*

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Maternal Full-Scale IQ†</th>
<th>Maternal Age at Conception, y</th>
<th>Maternal Assigned Plasma Phenylalanine Level, mg/dL</th>
<th>Maternal Education Less Than a High School Diploma, %</th>
<th>Subjects in 2 Lowest Levels of Social Position, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Who Received Preschool Evaluation (n = 253)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HPA control</td>
<td>71</td>
<td>101 (13)</td>
<td>29 (5)</td>
<td>.</td>
<td>3</td>
</tr>
<tr>
<td>Unreated MHP</td>
<td>33</td>
<td>95 (13)</td>
<td>23 (3)</td>
<td>.</td>
<td>10</td>
</tr>
<tr>
<td>Maternal metabolic control, wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior to pregnancy</td>
<td>17</td>
<td>91 (11)</td>
<td>29 (3)</td>
<td>22.5 (5.6)</td>
<td>13</td>
</tr>
<tr>
<td>&gt;0-10</td>
<td>26</td>
<td>83 (10)</td>
<td>27 (4)</td>
<td>23.0 (7.3)</td>
<td>14</td>
</tr>
<tr>
<td>&gt;10-20</td>
<td>47</td>
<td>83 (11)</td>
<td>25 (4)</td>
<td>24.3 (7.1)</td>
<td>19</td>
</tr>
<tr>
<td>&gt;20</td>
<td>59</td>
<td>80 (10)</td>
<td>23 (3)</td>
<td>26.4 (6.7)</td>
<td>36</td>
</tr>
<tr>
<td>Children Whose Preschool Evaluation Is Missing (n = 115)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HPA control</td>
<td>25</td>
<td>104 (13)</td>
<td>28 (4)</td>
<td>.</td>
<td>4</td>
</tr>
<tr>
<td>Unreated MHP</td>
<td>8</td>
<td>100 (1)</td>
<td>22 (4)</td>
<td>7.3 (1.8)</td>
<td>14</td>
</tr>
<tr>
<td>Maternal metabolic control, wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior to pregnancy</td>
<td>6</td>
<td>92 (6)</td>
<td>24 (2)</td>
<td>20.0 (6.4)</td>
<td>0</td>
</tr>
<tr>
<td>&gt;0-10</td>
<td>11</td>
<td>84 (15)</td>
<td>25 (5)</td>
<td>21.8 (5.8)</td>
<td>22</td>
</tr>
<tr>
<td>&gt;10-20</td>
<td>22</td>
<td>86 (10)</td>
<td>23 (4)</td>
<td>22.5 (7.6)</td>
<td>19</td>
</tr>
<tr>
<td>&gt;20 or never in control</td>
<td>43</td>
<td>80 (12)</td>
<td>22 (4)</td>
<td>26.7 (7.7)</td>
<td>36</td>
</tr>
</tbody>
</table>

*Values are expressed as mean (SD) unless otherwise indicated. Ellipses indicate data not available; HPA, hyperphenylalaninemia; and MHP, mild hyperphenylalaninemia.

†The number of subjects is 229 for children who received preschool evaluation and 76 for those whose preschool evaluation is missing.

### Table 3. McCarthy Scales of Children’s Abilities*

<table>
<thead>
<tr>
<th>Study Group</th>
<th>General Cognitive Index (GCI) Score</th>
<th>Percentage of Subjects With GCI Score</th>
<th>Subscale Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 86</td>
<td>≥ 72</td>
<td>Verbal</td>
</tr>
<tr>
<td>Non-HPA control</td>
<td>71</td>
<td>107 (20)</td>
<td>13</td>
</tr>
<tr>
<td>Unreated HPA</td>
<td>33</td>
<td>99 (14)</td>
<td>21</td>
</tr>
<tr>
<td>Maternal metabolic control, wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior to pregnancy</td>
<td>17</td>
<td>99 (13)</td>
<td>24</td>
</tr>
<tr>
<td>&gt;0-10</td>
<td>26</td>
<td>89 (17)</td>
<td>42</td>
</tr>
<tr>
<td>&gt;10-20</td>
<td>47</td>
<td>84 (18)</td>
<td>51</td>
</tr>
<tr>
<td>&gt;20 or never in control</td>
<td>59</td>
<td>71 (19)</td>
<td>78</td>
</tr>
</tbody>
</table>

*Values are expressed as mean (SD) unless otherwise indicated. HPA indicates hyperphenylalaninemia.
med somewhat better on tests measuring receptive language skills, with 40% attaining low scores on grammatical understanding and picture vocabulary.

Behavior. Within the behavioral domain, 30% (compared with the expected frequency of 18%) of the children received a rating in the clinical range on the total behavior problems index of the Achenbach Child Behavior Checklist. Their parents rated them as more external than internal \( t_{133} = 7.5; P < .001 \). They were less likely to be rated as withdrawn than as having problems with attention \( t_{133} = 2.9; P = .005 \) or social relationships \( t_{133} = 2.4; P = .02 \). Few children were rated as having somatic problems, anxiety, or delinquency.

The children appeared to develop appropriate social skills at a slower rate. On the Vineland Adaptive Behavior Scales, parents were somewhat more likely to note slower development in social relationships than in daily living skills \( t_{143} = 1.6; P = .12 \).

### Effect of Birth Order

Twenty-seven mothers treated for maternal PKU had more than one child enrolled in the study who received a preschool evaluation at age 4 years. On average, the children were 2.6 years apart in age. The mean difference in timing of maternal metabolic control was 2.2 weeks, with subsequent pregnancies being treated later than first pregnancies \( t = -0.96; P = .34 \). The mean GCI score for the later-born siblings was 6 points lower \( t = -1.6; P = .13 \).

### Results From 2-Year vs 4-Year Assessments

As noted in TABLE 5, for children born to women with PKU or MHP, scores on the McCarthy Scales at age 4 years were significantly lower than scores on the Bayley Scales at age 2 years. For children in the non-HPA comparison group, the differences were not significant.

### Comment

Delayed metabolic control in maternal PKU remains a serious problem. Treatment at any time during pregnancy appears to reduce the risks of cognitive impairment and developmental delay associated with untreated maternal PKU.

Children are best protected from elevated maternal phenylalanine levels when the woman attains metabolic control prior to pregnancy. There is no evidence for a safe zone once pregnancy begins that marks a period in which the fetus is fully protected.

While there is no doubt that maternal phenylalanine levels higher than 10 mg/dL (605 µmol/L) during pregnancy affect the fetus, levels lower than 10 mg/dL (605 µmol/L) are not associated with significant declines in GCI scores. However, the mean GCI scores of children born to mothers with untreated MHP were somewhat lower than that of children born to mothers in the non-HPA comparison group. While this might suggest some effect from MHP, the women in the non-HPA group included physicians and other health care professionals working at the medical centers.

### Table 4. Logistic Regressions for Risk of Low General Cognitive Index Score (≤86) in Treated Maternal Phenylketonuria Pregnancies (n = 132)*

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low maternal IQ (≤85 vs &gt;85)</td>
<td>2.9 (1.3-6.8)</td>
<td>.01</td>
</tr>
<tr>
<td>Maternal plasma phenylalanine level on normal diet (&gt;20 vs ≤20 mg/dL; &gt;1210 vs ≤1210 µmol/L)</td>
<td>2.5 (1.0-6.2)</td>
<td>.04</td>
</tr>
<tr>
<td>Low HOME Score (≤85 vs &gt;85 percentile)</td>
<td>2.0 (0.8-4.6)</td>
<td>.13</td>
</tr>
<tr>
<td>Weeks to metabolic control†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0-10</td>
<td>2.6 (0.6-11.3)</td>
<td>.20</td>
</tr>
<tr>
<td>&gt;10-20</td>
<td>3.2 (1.0-10.4)</td>
<td>.06</td>
</tr>
<tr>
<td>&gt;20 or never in control</td>
<td>7.4 (2.3-24.4)</td>
<td>.001</td>
</tr>
</tbody>
</table>

*HOME indicates Home Observation for Measurement of the Environment.
†Comparison vs metabolic control prior to pregnancy.

### Table 5. Comparisons Between Bayley Scales of Infant Development at Age 2 Years and McCarthy Scales of Children’s Abilities at Age 4 Years

<table>
<thead>
<tr>
<th>Maternal HPA Offspring ( n = 134 )</th>
<th>Control Subjects ( n = 53 )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bayley Scales</strong></td>
<td><strong>McCarthy Scales</strong></td>
</tr>
<tr>
<td><strong>Mental index</strong></td>
<td>96 (23) 49-151</td>
</tr>
<tr>
<td><strong>Motor index</strong></td>
<td>98 (19) 49-146</td>
</tr>
<tr>
<td><strong>Motor scale</strong></td>
<td>110 (16) 49-150</td>
</tr>
<tr>
<td><strong>General Cognitive Index</strong></td>
<td>114 (18) 58-151</td>
</tr>
<tr>
<td><strong>Percentage of Subjects &gt;1 SD Below Mean</strong></td>
<td>34</td>
</tr>
</tbody>
</table>

*For the comparison between the Bayley Scales and McCarthy Scales, \( P < .001 \) for mental index vs General Cognitive Index; \( P = .002 \) for motor index vs motor scale.
†For the comparison between the Bayley Scales and McCarthy Scales, \( P = .63 \) for mental index vs General Cognitive Index and motor index vs motor scale.
Their higher IQ and socioeconomic position might account for the somewhat higher scores among their offspring.

When maternal metabolic control is not attained until after pregnancy begins, neuropsychological functions are differentially impaired. The developmental profile of maternal PKU offspring shows a distinct trend toward lower scores on tests of language, memory, and quantitative abilities, while motor skills and behavior are relatively less affected. Whether this reflects a fundamental processing deficit or an underlying language deficit may be clearer in subsequent testing of the children.

The scores obtained when the children were 4 years old were lower than the scores on the infant development test. This is not an artifact of the tests, since the children in the non-HPA comparison group did not display a significant decline in scores. The decline in scores for maternal PKU children may presage an inability to meet increasing cognitive and language demands in the future.

This cohort of women with PKU experienced significant difficulties planning their pregnancies, attending scheduled medical appointments, complying with dietary restrictions, and monitoring their metabolic status. Adhering to the diet did not become easier with successive pregnancies. Pregnancies of later-born offspring were not within metabolic control sooner than earlier pregnancies and outcomes were not better. The women were often less able to maintain metabolic control, apparently not because of biological or genetic factors, but because of a lack of resources, time, motivation, support, and organization. This finding underscores the relevance of psychosocial factors in maternal PKU.

Methodologically, the study presented challenges for long-term follow-up and data interpretation. Tracking, treatment compliance, adherence to the study protocol, and follow-up rates varied between centers. The mothers of children for whom the preschool evaluation was missing were younger and had a higher average plasma phenylalanine level during pregnancy. This suggests that an even greater proportion of children might have been in the latest treated groups. Despite the possible impact of maternal IQ on offspring outcome, this variable could not be completely controlled for in the analyses since it was so highly correlated with metabolic control during pregnancy and with other maternal variables. Nonetheless, the results provide compelling evidence for the importance of strict treatment for maternal PKU.

One of the more interesting aspects of maternal PKU is its dissimilarity in outcome to PKU and its similarity in outcome to other prenatal conditions. For example, unlike maternal PKU offspring, children with PKU, whose exposure to elevated phenylalanine occurs postnatally, have deficits in the areas of visuomotor skills and fine motor speed. Untreated children with PKU are profoundly affected. They display autistic features or self-abusive behaviors. Children from late-treated or untreated maternal PKU pregnancies experience mental retardation, but not to a profound degree.

This observation suggests that the timing of exposure may determine the specific neuropsychological outcome. The literature on other maternal conditions also suggests that there may be effects in particular areas of functioning related primarily to timing and extent of exposure. For example, children born to women with high alcohol consumption are almost indistinguishable from children born to women with PKU. In fetal alcohol syndrome, studies have documented deficits in language, attention, memory, and information processing. As in maternal PKU, a clear dose-response relationship has been identified.

Interventions directed at reducing risks at each step in the maternal PKU cycle may prove to be most effective. In terms of outcome, every week counts. Previous studies documented the importance of social support in preventing unplanned (and hence late-treated) pregnancies in women with PKU. Camps, retreats, social support networks, newsletters, and other activities to enhance social support should be offered. The women may need hospitalization. Compliance can sometimes be improved through changes in formula or through the use of capsules containing the formula. In one home visitation program, mothers of children with PKU (called resource mothers) provided practical assistance and social support to pregnant women with PKU. A pilot study demonstrated that maternal metabolic control was achieved 4 weeks sooner and offspring outcome was significantly better in women who received the services of a resource mother.

After the infant's birth, the possibility that the home environment could moderate the adverse effects of maternal PKU should not be ignored. To date, extraordinary efforts are sometimes made to treat the woman during pregnancy, but then little assistance is offered following delivery. In this study, the postnatal environment was one of the stronger predictors of the GC1 score. This finding coincides with the earlier result that maternal PKU children from families with low HOME scores performed less well at 1 year than children from families with adequate home stimulation, despite their initial neonatal neurological rating. More research is needed to determine what interventions are effective in reducing risks for adverse outcomes before, during, and after pregnancy.

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In natural science, I have understood, there is nothing petty to the mind that has a large vision of relations, and to which every single object suggests a vast sum of conditions. It is surely the same with the observation of human life.

—George Eliot (1819-1880)