Neurodevelopmental Outcomes in Children With Hemifacial Microsomia

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Objective: To determine whether preadolescent children with hemifacial microsomia (HFM) have higher risk of neurodevelopmental delays than unaffected control individuals.

Design: Case-control follow-up study of neurodevelopment in children with and without HFM.

Setting: Case individuals were originally recruited from 26 craniofacial centers across the United States and Canada, and controls were recruited through community pediatricians.

Participants: One hundred thirty-six children with HFM (cases) and 568 unaffected children (controls).

Main Exposure: History of HFM.


Results: Children with HFM scored lower than controls on all measures (effect size = −0.27 to −0.45; P < .001 to P = .008). Compared with controls, cases were 2 to 3 times as likely to score in the at-risk range. Relative to controls, outcomes were worse for male cases and those whose mothers were 25 years or younger at the time of their birth. Cases with HFM plus other malformations had poorer outcomes, as did cases with hearing, vision, or speech impairments.

Conclusions: This is the first study, to our knowledge, to show that children with HFM have poorer neurodevelopmental outcomes than unaffected children, but further study using more detailed assessments is indicated. Clinically, the findings suggest that early neurodevelopmental screening is warranted for all children with HFM.

Arch Pediatr Adolesc Med. 2011;165(2):134-140

Hemifacial microsomia (HFM) refers to asymmetric hypoplasia of the face and ears. Structural outcomes range from isolated microtia to severe bilateral facial malformations.1-3 The origin of HFM is not fully understood, although hypotheses focus on aberrant neural crest cell activity and prenatal vascular disruption.4-6 Depending on the presence of associated malformations (eg, epibulbar dermoid and vertebral anomalies), other terms used to encompass HFM include oculoauricular vertebral syndrome and Goldenhar syndrome. Although differing origins for these presentations have been assumed, they are now thought to represent a spectrum of severity in a similar morphogenetic error.7 In addition to their differences in facial appearance, children with HFM have an increased risk of hearing loss, speech impairment, and feeding problems.8,9

Given the association between the developing face and brain,10 children with HFM have been thought to have neuropsychological deficits. Indeed, the few existing studies support this assumption.11,12 These investigations have been limited, however, by indirect assessment (eg, medical records reviews12) and small sample size.11 Furthermore, we are not aware of any studies that included unaffected control individuals, which is of concern because HFM is associated with demographic factors that might also influence neuropsychological outcomes.

This study tested the hypothesis that children with HFM exhibit worse verbal, nonverbal, and academic skills than controls. Potential moderators of outcome, such as child sex, maternal age, presence
or other malformations (aside from those included in the HFM phenotype), and history of speech, hearing, and vision impairment were also examined. Preliminary data for one outcome measure (teacher-reported academic competence) were reported previously for a subset of cases and controls.  

METHODS

STUDY PARTICIPANTS

Study participants were originally enrolled in infancy as part of a study of pregnancy risk factors for HFM. We attempted to reapproach these families for participation in the current study when their child reached 5 to 6 years of age. All participating children were between the ages of 5 and 12 years at study when their child reached 5 to 6 years of age. All participating children were between the ages of 5 and 12 years at enrollment.

CHILDREN WITH HFM

Cases included children with diagnoses of facial asymmetry or HFM, including oculoauricular vertebral syndrome, Goldenhar syndrome, or microtia. Exclusions were known chromosomal anomalies, mendelian inherited disorders, in utero isotretinoin exposure, having been adopted, and age older than 36 months. In the original cohort, 279 children with HFM were recruited from 26 craniofacial centers across the United States and Canada. We were unable to reapproach 12 case participants for the current study because of institutional review board constraints. An additional 62 children were excluded from this analysis for diagnostic reasons (40 with unilateral microtia and no other evidence of HFM, 11 twin gestations, 5 with isotretinoin-related HFM, and 6 with genetically inherited HFM). Nine families were excluded for other reasons, including child death. Of the remaining 196 eligible families, 43 could not be contacted and 17 refused participation or failed to return study materials, resulting in a final sample of 136 case participants (69.4% of eligible participants).

UNAFFECTED CONTROLS

Eight hundred fifty-four unaffected controls were recruited for the original study. Controls were recruited through cases' pediatricians (72.3%) or from another pediatric practice in close proximity and similar in size to those of cases' pediatricians (27.7%). Approximately 3 controls were recruited for each case. Controls were eligible for participation if they were within 2 months of the cases' age at the time of recruitment. In addition to the exclusions listed for cases, controls were excluded if they had any major malformation. Because of institutional review board constraints, we were unable to reapproach 43 control participants for the current study. Another 6 control families were excluded because of family circumstances and 2 were excluded because of twin gestation. Of the remaining 831 families, 142 could not be contacted and 121 refused participation, resulting in a final sample of 568 control participants (68.4% of eligible control children). One control child participated in the follow-up but did not provide data on any of the measures reported here.

MEASURES

The geographic distribution of our sample made it impractical to have a psychometrist assess each participant individually. We therefore selected 2 tests that teachers are qualified to administer, in accordance with the American Psychological Association's test user criteria: the Peabody Picture Vocabulary Test–Third Edition (PPVT-III) and the Beery-Buktenica Developmental Test of Visual Motor Integration–Fifth Edition (VMI-5). We also used questionnaire measures of teachers' and parents' impressions of children's academic status.

The PPVT-III

The PPVT-III is a norm-referenced measure of receptive vocabulary. Respondents are presented with increasingly difficult vocabulary words and shown 4 target pictures. They are asked to point to the picture that best represents the word. Reliability is excellent, and convergent validity is supported by strong correlations with other measures of verbal ability and prediction of academic achievement. The divergent validity of the PPVT-III is supported by low correlations with measures of visuomotor skill, including the VMI-5.

The VMI-5

The VMI-5 is a norm-referenced measure of perceptual motor abilities. Respondents copy a series of 24 increasingly difficult geometric designs, which are scored for accuracy by an examiner. The VMI-5 has good reliability, including strong test-retest stability and interscorer reliability among diverse examiners (eg, ranging from psychologists to teachers). Validity of the VMI-5 is supported by convergence with other measures of visual perception and low correlations (ie, divergence) with verbal measures.

Child Behavior Checklist and Teacher Report Form

Mothers and teachers completed the Child Behavior Checklist (CBCL) and Teacher Report Form (TRF), respectively. We used the Academic Competence scales from the CBCL and the TRF. These scales assess the child's academic achievement, history of special education services, and grade retention. Both measures have well-established reliability and validity.

DEMOGRAPHIC AND MEDICAL HISTORY INTERVIEW

Participating mothers were interviewed with regard to demographic, reproductive, and medical factors as part of the original study. Data used for this study included race and ethnicity and the following factors present at the time of birth: maternal age, maternal education, household income, marital status, primary language spoken in the home, and geographic region of residence.

MEDICAL RECORDS REVIEW

Medical records for cases were reviewed for notations of hearing, vision, and speech impairments and diagnoses of other malformations in addition to those that comprise the HFM spectrum (ie, auricular anomalies, dermoids, colobomas, and vertebral anomalies). The following categories of other malformations were found: cleft lip and/or palate (n=14), cardiac defect (n=26), renal anomaly (n=6), limb defect (n=7), gastrointestinal defect (n=5), genital malformation (n=6), Moebius syndrome (n=1), and Larsen syndrome (n=1).
Table 1. Demographic Factors for 136 Hemifacial Microsomia Case and 568 Control Individualsa

<table>
<thead>
<tr>
<th>Demographic Factor</th>
<th>Cases, No. (%)</th>
<th>Controls, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=136)</td>
<td>(n=568)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>87 (64.0)</td>
<td>283 (49.8)</td>
</tr>
<tr>
<td>Female</td>
<td>49 (36.0)</td>
<td>285 (50.2)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-6</td>
<td>52 (38.2)</td>
<td>224 (43.0)</td>
</tr>
<tr>
<td>7-8</td>
<td>71 (52.2)</td>
<td>278 (48.9)</td>
</tr>
<tr>
<td>9-10</td>
<td>13 (9.6)</td>
<td>45 (7.9)</td>
</tr>
<tr>
<td>11-12</td>
<td>0</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>92 (67.6)</td>
<td>429 (75.5)</td>
</tr>
<tr>
<td>White, Hispanic</td>
<td>33 (24.3)</td>
<td>67 (11.8)</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>4 (2.9)</td>
<td>49 (8.6)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (5.2)</td>
<td>23 (4.0)</td>
</tr>
<tr>
<td>Primary language spoken in the home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spanish</td>
<td>16 (11.8)</td>
<td>20 (3.5)</td>
</tr>
<tr>
<td>English</td>
<td>120 (88.2)</td>
<td>548 (96.5)</td>
</tr>
<tr>
<td>Homeschooled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (0.7)</td>
<td>14 (2.5)</td>
</tr>
<tr>
<td>No</td>
<td>135 (99.3)</td>
<td>554 (97.5)</td>
</tr>
<tr>
<td>Grade in school</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kindergarten</td>
<td>7 (5.2)</td>
<td>27 (4.8)</td>
</tr>
<tr>
<td>First</td>
<td>53 (39.0)</td>
<td>228 (40.1)</td>
</tr>
<tr>
<td>Second</td>
<td>37 (27.2)</td>
<td>137 (24.1)</td>
</tr>
<tr>
<td>Third</td>
<td>12 (8.8)</td>
<td>54 (9.5)</td>
</tr>
<tr>
<td>Fourth</td>
<td>9 (6.6)</td>
<td>18 (3.2)</td>
</tr>
<tr>
<td>Fifth or sixth</td>
<td>2 (1.5)</td>
<td>8 (1.4)</td>
</tr>
<tr>
<td>Missing</td>
<td>16 (11.8)</td>
<td>96 (16.9)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast/Mid-Atlantic</td>
<td>41 (30.2)</td>
<td>157 (27.6)</td>
</tr>
<tr>
<td>Midwest</td>
<td>36 (26.5)</td>
<td>167 (29.4)</td>
</tr>
<tr>
<td>South</td>
<td>22 (16.2)</td>
<td>90 (15.8)</td>
</tr>
<tr>
<td>West</td>
<td>37 (27.2)</td>
<td>154 (27.1)</td>
</tr>
<tr>
<td>Maternal age at birth, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25</td>
<td>35 (25.7)</td>
<td>142 (25.0)</td>
</tr>
<tr>
<td>&gt;25</td>
<td>101 (74.3)</td>
<td>426 (75.0)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/cohabiting</td>
<td>132 (97.1)</td>
<td>505 (88.9)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (2.9)</td>
<td>63 (11.1)</td>
</tr>
<tr>
<td>Maternal educational level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 y</td>
<td>21 (15.4)</td>
<td>56 (9.9)</td>
</tr>
<tr>
<td>High school graduate</td>
<td>28 (20.6)</td>
<td>116 (20.4)</td>
</tr>
<tr>
<td>Some college/technical school</td>
<td>37 (27.2)</td>
<td>135 (23.8)</td>
</tr>
<tr>
<td>College graduate</td>
<td>38 (27.9)</td>
<td>168 (29.6)</td>
</tr>
<tr>
<td>Graduate school</td>
<td>12 (8.8)</td>
<td>93 (16.4)</td>
</tr>
<tr>
<td>Annual household income, $</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 000</td>
<td>32 (23.5)</td>
<td>92 (16.2)</td>
</tr>
<tr>
<td>25 000-64 999</td>
<td>47 (34.6)</td>
<td>247 (43.5)</td>
</tr>
<tr>
<td>≥65 000</td>
<td>44 (32.4)</td>
<td>199 (35.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>13 (9.6)</td>
<td>30 (5.3)</td>
</tr>
</tbody>
</table>

a Percentage calculated for known values only. Percentages may not total 100 because of rounding.

PROCEDURES

Mothers were initially contacted by telephone and those who expressed interest in participating were mailed a study packet, which included the CBCL. Mothers who consented to participate identified a teacher who could administer tests to the child and complete questionnaires. In a few instances (n = 19), a classroom teacher was not available, so the family identified a similarly trained adult (eg, a speech therapist or school counselor). Study personnel then contacted the child’s teacher and sent a packet that included the TRF, PPVT-III, and VMI-5 test materials and written instructions for administration. To reduce errors, directions for administering the PPVT-III and VMI-5 were modified, and rather than scoring measures themselves, teachers mailed the completed forms to study personnel, who were masked to case status, for review and scoring. If significant administration errors were found (n = 3 cases, n = 12 controls), the same teacher or another teacher identified by the family was contacted and asked to readminister part or all of the testing as needed. This study was approved by the Boston University Institutional Review Board and completed in full compliance with Health Insurance Portability and Accountability Act standards.

DATA ANALYSIS

Demographic and clinical characteristics were summarized separately for HFM cases and controls using descriptive statistics. To evaluate for response bias, we calculated descriptive statistics for demographic variables separately for participants and nonparticipants. Linear regression analyses were used to compare children with HFM and unaffected controls on the various outcome measures, adjusting for child’s sex, child’s age at testing, mother’s race (white, black, or other), mother’s ethnicity (Hispanic vs non-Hispanic), maternal age at the time of the child’s birth (≤25 years vs >25 years), maternal education (<12th grade, 12th-grade graduate, some college, or college graduate), household income (<$25 000, $25 000-$34 999, $35 000-$64 999, ≥$65 000, or not reported), marital status (single and living with child’s father; single and not living with child’s father; divorced, separated, or widowed; or other), primary language spoken in the home (English or Spanish), and geographic region of residence (Northeast, Mid-Atlantic, Midwest, South, or West). Standard scores, with a normative mean of 100 and an SD of 15, were used for comparison on the PPVT-III and VMI-5. On the CBCL and TRF, T scores were used (normative mean = 50, SD = 10). The magnitudes of group differences were estimated using standardized mean difference effect sizes (comparable to Cohen’s d). Adjusted for demographics. Inverse probability weighting (IPW) was used to determine whether these findings were influenced by response bias. For these analyses, we first used logistic regression to predict participation using the listed covariates. We then generated scores reflecting the probability of each participant being observed (ie, participating) in the current study. Linear regression analyses were then rerun, weighted by the inverse of the probability of being observed. We also examined scores categorically, using clinical cutoff scores of greater than 1 SD below the normative mean to identify children at risk for developmental problems (ie, <85 for the PPVT-III and VMI-5 and <40 for the CBCL and TRF). Odds ratios (ORs) were calculated to compare the proportion of cases vs controls scoring below this at-risk level. Again, IPW was used to determine whether the findings were influenced by response bias.

We also examined case-control group differences separately by sex and maternal age at the time of the child’s birth (maternal age ≤25 years vs >25 years), controlling for the same listed demographic variables. The cutoff maternal age of 25 years was chosen based on the distribution of maternal age in our sample. Finally, we examined outcomes separately for case subgroups, including cases with other malformations and those with hearing, speech, or visual impairment. All these conditions are closely related to HFM, and subgroup differences may help to identify children at particular risk and select targets for intervention.
Table 2. Case-Control Comparisons of Neurocognitive Test Scoresa

<table>
<thead>
<tr>
<th>Measure</th>
<th>No. of Case/Control Individuals</th>
<th>Mean (SD) Score</th>
<th>Unweighted Case-Control Difference in Scores (95% CI)b</th>
<th>Inverse-Probability Weighted Case-Control Difference in Scores (95% CI)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPVT-III</td>
<td>120/469</td>
<td>97.39 (20.31)</td>
<td>-6.76 (-9.70 to -3.82)</td>
<td>-8.99 (-13.12 to -4.86)</td>
</tr>
<tr>
<td>VMI-5</td>
<td>116/468</td>
<td>92.84 (11.21)</td>
<td>-3.30 (-5.56 to -1.05)</td>
<td>-3.70 (-6.04 to -1.37)</td>
</tr>
<tr>
<td>CBCL school</td>
<td>132/552</td>
<td>44.15 (8.45)</td>
<td>-3.31 (-4.73 to -1.88)</td>
<td>-3.82 (-5.65 to -1.98)</td>
</tr>
<tr>
<td>TRF Academic Competence</td>
<td>124/497</td>
<td>48.19 (9.12)</td>
<td>-2.25 (-3.89 to -0.62)</td>
<td>-3.92 (-4.88 to -1.16)</td>
</tr>
</tbody>
</table>


aTRF and CBCL: T scores, with a normative mean of 50 and an SD of 10; VMI and PPVT: standard scores, with a normative mean of 100 and an SD of 15.

bIn addition to case-control status, regression models included terms for child’s sex, child’s age at testing, mother’s race (white, black, or other), mother’s ethnicity (Hispanic vs non-Hispanic), maternal age, maternal education (<12th grade, 12th-grade graduate, some college, or college graduate), household income (<$25 000, $25 000-$34 999, $35 000-$41 999, or not reported), marital status (single and living with child’s father; single and not living with child’s father; divorced, separated, or widowed; or other), primary language spoken in the home (English or Spanish), and geographic region of residence (Northeast/Mid-Atlantic, Midwest, South, or West).

cAnalyses weighted for demographic characteristics and other listed covariates.

Demographic characteristics of the sample are summarized in Table 1. Relative to controls, the case group had a higher proportion of males (64.0% vs 49.8% in the control group) and people of Hispanic ethnicity (24.3% vs 11.8% in the control group) and were more likely to come from primarily Spanish-speaking households (11.8% vs 3.5% in the control group). Homeschooling was infrequent in both groups (0.7% of cases and 2.9% of controls), and most children were in kindergarten through second grade (72.4% of cases and 69.0% of controls). Average age was similar in both groups (mean [SD] age, 7.0 [1.0] years in the case group vs 6.9 [1.0] years in the control group). Socioeconomic status was similar for the 2 groups, with most mothers having completed some postsecondary education (63.9% of cases and 69.6% of controls) and reporting an annual household income of $25 000 per year or more (67.0% of cases and 78.5% of controls). Geographic region was similar for both groups. Of the cases, 33.8% had 1 or more documented malformations other than those related to HFM. Speech and hearing impairments were documented for 47.1% and 55.1% of cases, respectively, and vision impairment was documented for 16.9%. Seventy percent of cases had at least 1 of these problems.

Compared with participants, mothers of cases and controls who did not respond or declined participation had lower educational attainment (58.8% high school graduate or less) and were less likely to be white (41.5%). These differences were more apparent for case mothers, for whom nonparticipants were more likely to be Hispanic (45.8%), to have a daughter (48.6%), and to have a high school education or less (63.9%) compared with participating cases.

Comparison of Cases and Controls on Neurodevelopmental Outcomes

Regression analyses revealed statistically significant group differences on the PPVT-III (P < .001) and VMI-5 (P = .004) (Table 2). The adjusted group differences on the VMI and PPVT-III were small to moderate (effect size = −0.31 to −0.43). Similarly, children with HFM received lower scores on average than controls on the Academic Competence scales of the CBCL (P < .001) and TRF (P = .008). Again, the magnitude of these effects was small to moderate (effect size = −0.27 to −0.45). Differences increased in magnitude with the application of IPW to adjust for baseline bias (Table 2).

When examining scores categorically, children with HFM were approximately 3 times as likely to score in the at-risk range on the PPVT-III (OR, 4.16; 95% confidence interval [CI], 2.01-8.59) and twice as likely on the VMI-5 (2.23; 1.19-4.20). On the TRF and CBCL, children with HFM were twice as likely to score in the at-risk range (TRF: OR, 2.57; 95% CI, 1.45-4.56; CBCL: 2.44; 1.46-4.07). The magnitude of these associations increased with the application of IPW (results not shown).

Subgroup Analyses

Cases received lower scores than controls on all measures, regardless of the child’s sex or the mother’s age (Figure 1). Differences were consistently larger for children whose mothers were 25 years or younger at the time of their birth than children whose mothers were older than 25 years, and differences tended to be larger for boys than girls. Associations were strongest for cases with other malformations (Figure 2). Cases with speech impairment had worse outcomes on all measures, whereas those with hearing loss or vision impairment had worse outcomes on some measures but not others.

Comment

These findings support the hypothesis that children with HFM exhibit poorer verbal, nonverbal, and academic skills than unaffected controls. Receptive language and scholastic competence were areas of particular vulnerability, with clinically meaningful differences observed in both domains. For example, children with HFM were 3 times as likely to score in the at-risk range of performance on the PPVT-III, implying that they are more likely than their peers to require specialized
neurodevelopmental problems than females (eg, au-
less access to needed intervention services. Consistent
be particularly difficult because younger mothers may have
sion of a young mother and medical vulnerability may
other craniofacial malforma-
tions.22 These other malformations may indicate greater
populations who have other craniofacial malforma-
tions, and the sociopsychological effects of anomalous
craniofacial appearance (eg, negative social bias may affect
vessels, other craniofacial malformations.22 These other malformations may indicate greater
severity in the underlying morphologic error responsible for HFM, which may also be reflected in central ner-
vous system development. Relative to controls, worse out-
comes were also observed for cases whose mothers were
25 years or younger at the time of their birth, even after
adjusting for anticipated confounds (eg, socioeconomic
status). Younger maternal age has been linked with worse
neurodevelopmental and academic outcomes in previ-
ous studies.21,24 For children with HFM, the combina-
tion of a young mother and medical vulnerability may be particularly difficult because younger mothers may have
less access to needed intervention services. Consistent
with research showing males to be more vulnerable to
neurodevelopmental problems than females (eg, au-
tism,25 dyslexia,26 and language delay27), on most mea-
sures boys with HFM were more likely than girls to score
lower than controls. Speech impairment was associated
with lower scores among cases; associations among chil-
ren with vision and hearing impairments, on the other
hand, were less consistent.

Our findings extend the results of 2 previous, smaller
studies11,12 in which comparisons with test norms or the
frequency of documented learning problems suggested
that children with HFM had an elevated risk of poor out-
comes. Although the association between HFM and com-
promised neurodevelopment appears more certain in this
study, the mechanism(s) accounting for this relation re-
main(s) poorly understood. Several factors associated with
HFM are potentially contributory, including speech and
hearing difficulties, vision impairments, central ner-
vous system anomalies, operations and hospitaliza-
tions, and the sociopsychological effects of anomalous
craniofacial appearance (eg, negative social bias may affect
teachers' ratings of academic competence).28 Our sub-
group analyses suggest that some of these conditions are
associated with poorer outcomes even if they do not fully
account for the association between HFM and neurode-
velopmental delay. This study addressed the limitations
of prior investigations through the inclusion of a large
sample of children with HFM and demographically simi-
lar controls. In addition, ours is one of the few projects to
use standardized assessments (vs reliance on clinical
impressions or medical records), which broadens the in-
terpretability and generalization of our findings.

With respect to this study's limitations, families with
higher social risk were underrepresented in this follow-up
study, and IPW analyses suggest that group

Figure 1. Case-control comparisons of neurodevelopmental test scores
within strata defined by child’s sex and mother’s age. Covariate adjusted
standardized mean difference effect sizes and 95% confidence intervals are
shown. CBCL, Child Behavior Checklist; PPVT-III, Peabody Picture

Figure 2. Case-control comparisons of neurodevelopmental test scores for
subgroups. Covariate-adjusted standardized mean difference effect
sizes and 95% confidence intervals are shown. CBCL, Child Behavior
Checklist; PPVT-III, Peabody Picture Vocabulary Test–Third Edition; TRF,
Teacher Report Form; VMI-5, Beery-Buktenica Developmental Test of
differences may be even larger among children from lower socioeconomic statuses and racial/ethnic minority backgrounds. Another limitation relates to our assessment battery, which consisted of 2 screening measures, parent and teacher report measures of academic competence, and a review of cases’ medical records. As a result, we are unable to evaluate several important neurodevelopmental domains (eg, global IQ and expressive language) or to directly assess academic achievement. Furthermore, assessments were completed by children’s teachers rather than psychometrists. Although this method allowed us to efficiently assess a geographically diverse sample, this likely reduced the consistency of test administration. We have no reason to suspect that errors were more likely in one group than the other and, if anything, a higher test error rate would reduce the likelihood of detecting group differences. Finally, reliance on medical records is inherently problematic because of inconsistent documentation of associated conditions. The phenotype of HFM varies substantially, which may have implications for neurodevelopmental outcome.不幸,因为我们被限制于信息的可获取性，在医学记录中，我们无法从发育障碍中获取发展性差异作为一个因素的HFM严重程度或其全范围相关的特征。此外，我们的研究结果表明，部分的领域需要在未来的研究中被直接地评估。

Future studies of children with HFM are needed to articulate their neuropsychological profile. Longitudinal studies, which follow up cases and controls from infancy, are likely to be particularly useful because these projects may lend insight into the risk factors that modify or mediate neurodevelopmental risk. Such research will have direct clinical relevance, helping to identify areas of need for educational and psychological interventions. In addition, such studies will advance our theoretical understanding of the origins of developmental delay in this population and the association between the developing face and brain (eg, are certain craniofacial malformations associated with particular neuropsychological deficits?). As an initial step, using data from this cohort, we plan to examine the contribution of pregnancy factors implicated in the etiology of HFM (eg, vascular disruption and maternal diabetes mellitus) on neuropsychological outcomes in an effort to generate hypotheses to guide future research. We also plan to follow up cases and controls into adolescence, with anticipated studies of neuropsychological function, craniofacial phenotype, and brain morphology.

In conclusion, these findings suggest that children with HFM have an elevated risk of delays in receptive language, visuomotor skill, and academic function. Clinically, these early-stage findings suggest that routine neurodevelopmental screening is warranted in this population. Early detection and management of speech, hearing, and vision impairments may help to offset some of the elevated risk in children with HFM.

Accepted for Publication: July 27, 2007.

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Author Contributions: Drs Collett, Speltz, and Werler had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Speltz and Werler. Acquisition of data: Speltz and Werler. Analysis and interpretation of data: Collett, Speltz, Cloonan, Leroux, Kelly, and Werler. Drafting of the manuscript: Collett and Werler. Critical revision of the manuscript for important intellectual content: Collett, Speltz, Cloonan, Leroux, Kelly, and Werler. Obtained funding: Speltz and Werler. Administrative, technical, and material support: Speltz, Cloonan, and Werler. Study supervision: Speltz.

Financial Disclosure: None reported.

Funding/Support: This publication was made possible in part by grant R01 DE 11939-07 from the National Institute of Dental and Craniofacial Research (NIDCR) to Dr Werler.

Disclaimer: The contents of this article are solely the responsibility of the authors and do not necessarily represent the official view of NIDCR or the National Institutes of Health.

Additional Contributions: We thank Sandra Hatfield, BA, Marguerite Dembro, BA, Jane Sheehan, RN, MSN, and Lisa Crowell, RN, for their help conducting the study and Sharan Conner, MA, and Diana Prise, BA, for their help with data scoring and processing.

**Announcement**

**Trial Registration Required.** In concert with the International Committee of Medical Journal Editors (ICMJE), Archives of Pediatrics and Adolescent Medicine will require, as a condition of publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorials by DeAngelis et al in the September 8, 2004 (2004;292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of JAMA. Also see the Instructions to Authors on our Web site: www.archpediatrics.com.