Facial Dysmorphism Across the Fetal Alcohol Spectrum

OBJECTIVE: Classic facial characteristics of fetal alcohol syndrome (FAS) are shortened palpebral fissures, smooth philtrum, and thin upper vermilion. We aim to help pediatricians detect facial dysmorphism across the fetal alcohol spectrum, especially among nonsyndromal heavily exposed (HE) individuals without classic facial characteristics.

METHODS: Of 192 Cape Coloured children recruited, 69 were born to women who reported abstaining from alcohol during pregnancy. According to multifaceted criteria, the remainder were allocated clinically to the FAS (n = 22), partial FAS (n = 26) or nonsyndromal HE (n = 75) categories. We used dense surface modeling and signature analyses of 3-dimensional facial photographs to determine agreement between clinical categorization and classifications induced from face shape alone, to visualize facial differences, and to consider predictive links between face shape and neurobehavior.

RESULTS: Face classification achieved significant agreement with clinical categories for discrimination of nonexposed from FAS alone (face: 0.97–1.00; profile: 0.92) or with the addition of partial FAS (face: 0.90; profile: 0.92). Visualizations of face signatures delineated dysmorphism across the fetal alcohol spectrum and in half of the nonsyndromal HE category face signature graphs detected facial characteristics consistent with prenatal alcohol exposure. This subgroup performed less well on IQ and learning tests than did nonsyndromal subjects without classic facial characteristics.

CONCLUSIONS: Heat maps and morphing visualizations of face signatures may help clinicians detect facial dysmorphism across the fetal alcohol spectrum. Face signature graphs show potential for identifying nonsyndromal heavily exposed children who lack the classic facial phenotype but have cognitive impairment. Pediatrics 2013;131:e779–e788
Prenatal alcohol exposure causes a continuum of effects. The most severe phenotype, fetal alcohol syndrome (FAS), affects face shape, growth, and neurobehavior. Fetal alcohol spectrum disorders (FASDs) include FAS and other pathologies arising from prenatal alcohol exposure. Table 1 summarizes criteria we used to characterize FAS and partial FAS (PFAS) and to differentiate them from those with nonsyndromal heavy alcohol exposure (HE), where our criteria were not met, and from nonexposed controls (HCs). Classic FAS facial characteristics of short palpebral fissures, smooth philtrum, and thin upper lip vermillion overlap with conditions that pediatricians consider as differential diagnoses (Table 2).

Several studies have explored image-based recognition of FAS facial features. Often, the use of linear measures alone limited shape analysis. We used sparse landmarks to induce a correspondence of 25,000+ points on a face enabling dense surface model (DSM) analysis of shape. Previously, such analyses delineated facial features in neurodevelopmental disorders establishing discriminating characteristics and phenotype-genotype correlations, where the incidence of heavy alcohol use during pregnancy and FAS are among the highest in the world. In one cohort (N = 137), drinking histories of mothers were obtained prospectively by using a timeline follow-back interview administered at recruitment in antenatal clinics, during pregnancy, and at 6 weeks postpartum, to ascertain third trimester drinking. Heavy drinkers consumed 14 standard drinks per week or participated in binges of ≥5 drinks per occasion. Controls reported abstaining from drinking during pregnancy. Alcohol-consuming pregnant women were advised to modify intake and referred for help. In the second cohort (N = 55), 24 children were older siblings of children in the first cohort. The remainder, alcohol exposed and controls, were identified by screening children in a school in a rural area with high incidence of alcohol abuse. Ethical approval was obtained at Wayne State University and UCT. Written informed consent was obtained from mothers and oral assent was obtained from children.

Clinical and Neurobehavioral Assessments

We organized a community clinic in which each child was examined for growth deficits and FAS facial features independently by expert dysmorphologists (H.E.H., L.K.R.) blinded to prenatal alcohol exposure history, using a standard protocol and the Astley Lip-Philtrum Guide. There was substantial agreement between them on assessment of dysmorphism, including published philtrum and vermilion rating scales and palpebral fissure length (r = 0.80, 0.84, and 0.77, respectively), and between them and another dysmorphologist (N.K.) who examined a small subset not seen at the clinic (median r = 0.78).

METHODS

Participants

The 192 participants were from 2 longitudinal University of Cape Town (UCT) cohorts recruited from the local Cape coloured (mixed ancestry) community, where the incidence of heavy alcohol use during pregnancy and FAS are among the highest in the world. In one cohort (N = 137), drinking histories of mothers were obtained prospectively by using a timeline follow-back interview administered at recruitment in antenatal clinics, during pregnancy, and at 6 weeks postpartum, to ascertain third trimester drinking. Heavy drinkers consumed 14 standard drinks per week or participated in binges of ≥5 drinks per occasion. Controls reported abstaining from drinking during pregnancy. Alcohol-consuming pregnant women were advised to modify intake and referred for help. In the second cohort (N = 55), 24 children were older siblings of children in the first cohort. The remainder, alcohol exposed and controls, were identified by screening children in a school in a rural area with high incidence of alcohol abuse. Ethical approval was obtained at Wayne State University and UCT. Written informed consent was obtained from mothers and oral assent was obtained from children.

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Face Analysis

All 3-dimensional (3D) facial images were captured with a commercial photogrammetric camera (3dMD Inc, Atlanta). One author (M.S.) landmarked each image at 24 validated locations (Supplemental Fig 1). A DSM constitutes principal component analysis modes covering 99% of...
shape variation in the faces analyzed. Landmarking and DSM building were undertaken using software developed in-house. The agreement of clinical categorization (Table 1) and classification using DSM representation of face shape was estimated from 20 random 90% to 10% training-unseen test pairs of subject subsets (stratified with respect to affected or unaffected status) by using receiver operating characteristic (ROC) curve analysis. To analyze the faces of those who were HE, we introduced signature graph drawn using GraphViz.

**RESULTS**

**Sample Characteristics**

The 96 male and 96 female children had no sex or age distribution differences (Table 3). Drinking levels among HE groups did not differ statistically. Alcohol-consuming mothers reported an average of 2.8 standard drinks per day.

**TABLE 1 Clinical Categorization**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>FAS</th>
<th>PFAS</th>
<th>HE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol exposure</td>
<td>Confirmed maternal consumption throughout gestation</td>
<td></td>
<td>≥1 oz AA/d or ≥4 binges: each ≥2 oz AA</td>
</tr>
<tr>
<td>Face</td>
<td>Short palpebral fissure (≤10th percentile)</td>
<td>≥2 of 3</td>
<td>≥2 of 3</td>
</tr>
<tr>
<td></td>
<td>Thin upper lip (4 or 5 on Astley scale)</td>
<td>Smooth philtrum (4 or 5 on Astley scale)</td>
<td></td>
</tr>
<tr>
<td>Growth</td>
<td>Delay for height or weight (≤10th percentile)</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Head/Brain</td>
<td>Reduced circumference (≤10th percentile)</td>
<td>≥1 of 2</td>
<td>≥1 of 3</td>
</tr>
<tr>
<td></td>
<td>CNS structural abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavior</td>
<td>Evidence of behavioral or cognitive deficiency</td>
<td>—</td>
<td>≥1 of 3</td>
</tr>
</tbody>
</table>

AA, absolute alcohol; 1 oz AA = 2 standard drinks.

A paucity of controls forced gender aggregation when normalizing. Displacement orthogonal to the face surface at 25,000+ points was normalized with respect to displacements at corresponding points on age-matched reference faces to produce a face signature. Analogous processes produced signatures for lateral, vertical, and depth axes. Face signatures were visualized as heat maps to depict normalized contraction, coincidence, and expansion compared with matched controls. For a pair of signatures, face signature distance (FSD) calculated the difference in facial dysmorphism as the square root of summed squared differences across all surface points. Each face signature was linked to another with shortest FSD from it, generating signature clusters themselves linked by closest constituent signatures to form a connected signature graph drawn using GraphViz.

**TABLE 2 Conditions to Be Considered as a Differential Diagnosis for FASD**

<table>
<thead>
<tr>
<th>Syndrome/Condition</th>
<th>Features Overlapping With FASD</th>
<th>Differentiating Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aarskog</td>
<td>Small nose with anteverted nares, broad philtrum, maxillary hypoplasia, and wide-spaced eyes</td>
<td>Rounded face, down-slanted palpebral fissures, widow’s peak, crease below lower lip, incomplete out folding of upper eyelids, and dental eruption problems</td>
</tr>
<tr>
<td>Cornelia de Lange</td>
<td>Long philtrum, thin vermilion border, anteverted nares, and depressed nasal bridge</td>
<td>Single, bushy eyebrow extending across forehead, long eyelashes, downturned mouth, high arched palate, and short limbs/stature</td>
</tr>
<tr>
<td>Dubowitz</td>
<td>Short palpebral fissures, wide spaced eyes, and epicanthal folds</td>
<td>Shallow supraorbital ridge with nasal bridge near the level of the forehead, and broad nasal tip</td>
</tr>
<tr>
<td>Fetal hydantoin</td>
<td>Wide-spaced eyes and depressed nasal bridge</td>
<td>Short nose with bowed upper lip</td>
</tr>
<tr>
<td>Fetal valproate</td>
<td>Epicantal folds, anteverted nares, long philtrum with thin vermilion border, and wide-spaced eyes</td>
<td>High forehead, infraorbital crease or groove, and small mouth</td>
</tr>
<tr>
<td>Maternal phenylkeonuria</td>
<td>Epicantals, short palpebral fissures, long underdeveloped philtrum, and thin vermilion border</td>
<td>Small upturned nose, round facies, and prominent glabella</td>
</tr>
<tr>
<td>Noonan</td>
<td>Low nasal bridge, wide spaced eyes, and epicanthal folds</td>
<td>Down-slanted palpebral fissures, keratoconus, wide mouth, and protruding upper lip</td>
</tr>
<tr>
<td>Toluene embryopathy</td>
<td>Short palpebral fissures, mid-face hypoplasia, smooth philtrum, and thin vermilion border</td>
<td>Mikrognathia, large anterior fontanel, down-turned mouth corners, hair patterning and ear abnormalities, and bifrontal narrowing</td>
</tr>
<tr>
<td>Williams</td>
<td>Short palpebral fissures, anteverted nares, long philtrum, depressed nasal bridge, and epicanthal folds</td>
<td>Wide mouth with full lips, stellate pattern of the iris, periorbital fullness, and connective tissue disorders</td>
</tr>
</tbody>
</table>

TABLE 3 Sample Characteristics (N = 192)

<table>
<thead>
<tr>
<th></th>
<th>FAS (n = 22)</th>
<th>PFAS (n = 26)</th>
<th>HE (n = 75)</th>
<th>HC (n = 69)</th>
<th>F or χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at 3D photo (years)</td>
<td>10.6 ± 2.4</td>
<td>10.0 ± 1.5</td>
<td>10.4 ± 2.7</td>
<td>10.1 ± 2.6</td>
<td>0.46</td>
</tr>
<tr>
<td>Sex (males %)</td>
<td>12 (64.5%)</td>
<td>14 (53.8%)</td>
<td>36 (48.0%)</td>
<td>34 (49.5%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Palpebral fissures</td>
<td>2.9 ± 1.4</td>
<td>2.8 ± 1.3</td>
<td>2.7 ± 1.0</td>
<td>2.0 ± 1.2</td>
<td>0.87***</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>127.0 ± 13.1</td>
<td>131.0 ± 10.4</td>
<td>136.6 ± 13.6</td>
<td>135.6 ± 14.1</td>
<td>3.68*</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>25.8 ± 7.2</td>
<td>27.8 ± 6.4</td>
<td>34.0 ± 10.9</td>
<td>34.2 ± 13.2</td>
<td>5.29**</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>49.9 ± 1.4</td>
<td>51.6 ± 1.3</td>
<td>53.0 ± 1.7</td>
<td>53.0 ± 1.9</td>
<td>22.55***</td>
</tr>
<tr>
<td>BMI</td>
<td>15.7 ± 1.6</td>
<td>16.0 ± 1.3</td>
<td>17.8 ± 3.2</td>
<td>18.0 ± 3.9</td>
<td>5.05**</td>
</tr>
<tr>
<td>Facial anomalies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short palpebral fissures</td>
<td>18 (81.8%)</td>
<td>18 (69.2%)</td>
<td>9 (12.0%)</td>
<td>8 (11.6%)</td>
<td>72.89***</td>
</tr>
<tr>
<td>Flat philtrum</td>
<td>20 (90.9%)</td>
<td>25 (96.2%)</td>
<td>22 (29.3%)</td>
<td>15 (21.7%)</td>
<td>69.13***</td>
</tr>
<tr>
<td>Thic vermilion</td>
<td>20 (90.9%)</td>
<td>25 (96.2%)</td>
<td>20 (26.7%)</td>
<td>17 (24.6%)</td>
<td>68.34***</td>
</tr>
<tr>
<td>Child's WISC IV-IQ</td>
<td>60.6 ± 11.1</td>
<td>65.3 ± 10.4</td>
<td>71.1 ± 12.8</td>
<td>75.3 ± 12.0</td>
<td>7.82***</td>
</tr>
</tbody>
</table>

Values are mean ± SD or %. AA, absolute alcohol; 1 oz AA ≈ 2 standard drinks. Cut-points for facial anomalies: short palpebral fissures: ≤10th percentile; flat philtrum and thin vermilion, rank 4 or 5 on Astley Lip-Philtrum Guide 1. The palpebral fissure measurements were obtained by using a rigid ruler, marked in millimeters according to standard methods, and were compared with published norms; centiles were recorded. Mothers of PFAS and HE children smoked more than mothers of controls (P <= .05 and .01, respectively). Mothers of FAS and PFAS children were higher in parity than were mothers of children with HE and controls (all P < .01). Maternal age at delivery for FAS children was higher than for mothers of children with HE and HCs (P <= .01) and PFAS compared with children with HE (P < .05). Dose-dependent relations for head circumference: FAS < PFAS < HE and controls (P < .001); height and weight: FAS < HE and controls (P < .01); weight: PFAS < HE and controls (P < .01). WISC IQ: FAS < HE and controls (P < .002); PFAS < controls (P < .002); PFAS < HE (P = .055); HE < controls (P < .10). FAS and PFAS < controls (P < .0005); FAS < HE (P < .0005); HE < controls (P < .10).

* P < .05.
** P < .01.
*** P < .001.

Mean Facial Growth and Dysmorphism Across the Fetal Alcohol Spectrum

In a face DSM with mixed age range, the first principal component (PC1) reflects growth. Compared with HCs, the FAS group showed significantly reduced facial growth (Fig 1A) not attributable to difference in age distribution in different categories (Table 3). The PFAS difference from HCs was less (Fig 1A) and marginal for those with HE (Fig 1B). This reduced growth caused heat maps of average FAS and PFAS faces to be almost monochromatic. Because growth retardation is discriminating in FASD, we built size and shape DSSMs. When size difference overpowers subtle shape difference, we sometimes scale average faces before comparing shape. Here, FAS, PFAS, and HE average faces were scaled using nasion-gnathion ratios, to provide shape-only comparisons (Fig 2A). Blue regions on the upper lip indicate convexity of the philtral groove, reflecting smoothness. Lower thresholds of significance for PFAS and HE groups reflect more subtle effects. In the lateral axial heat map of the average FAS face, opposing red-blue colors near inner and outer canthi confirm shortened palpebral fissures (Fig 2B). The vertical comparison reflects reduced length and upward displacement of the nose. The depth comparison identifies flat nasal bridge and glabella, malar flattening (yellow anterior zygomatic arch), and micrognathia and retrognathia (red chin). Upper lip protrusion and malar flattening during pregnancy with concentrated drinking during weekends and an average consumption per occasion of 8.9 drinks. Twelve mothers reported using marijuana, 1 used cocaine, and 3 used methaqualone (“mandrax”). A majority (70.8%) smoked, with 16.7% smoking an average of >10 cigarettes per day. On the 3D image capture, there were dose-dependent effects: for head circumference, FAS < PFAS < HE and controls; for height and weight, FAS < HE and controls; and for weight, PFAS < HE and controls. Low IQ scores seen in each group reflect poor education and socioeconomic deprivation in this community.31,32 As expected, WISC-IV IQ scores of exposed children were lower than those of controls. The children categorized as FAS or PFAS were substantially more likely to meet clinical dysmorphism criteria than were those of the HE or control groups.
suggest rotational effects at the premaxilla. These features are clearly seen in the morph (Supplemental Movie 1).

**Signature Visualizations Reveal Individual Facial Dysmorphism**

Figure 2C shows portrait and profile views of a child with FAS, selected because he has classic features as well as idiosyncratic mild proptosis. The first heat map pair shows the raw difference from the mean of 35 age-matched controls, with green indicating surface coincidence and red-blue indicating $\pm 5$ mm contraction and expansion. The second pair shows how raw differences of reduced face width and proptosis are reversed in relative magnitude after normalization. Philtral smoothness is delineated by blue on the upper lip. To reveal some features, the sensitivity of the heat map significance scale needs to be altered. Alternatively, a DSM of a more restricted area can reveal localized dysmorphism. For example, Fig 3 shows how upper lip signatures reveal where and to what degree philtral grooves are more convex and smooth. Heat maps highlighted facial dysmorphism, but the most effective visualizations were dynamic morphs between individuals and matched controls (Supplemental Movie 2). The portrait morph emphasized reduced zygomatic and gonial width, inner canthal folds, increased nose width, and philtral smoothness, especially adjacent to the columella. The profile morph highlighted flat nasal bridge and malar region, short nose, philtral groove convexity, and retrognathia.

**Agreement with HC, FAS, and PFAS Categorization Based on Face Shape Alone**

Closest mean (ie, relative similarity to average HC or FAS faces) induced a classification of both groups. Twenty randomly sampled 90% to 10% training-unseen test set pairs gave a mean agreement of 0.967 (Table 4) corresponding to the probability of correctly classifying a pair of faces: 1 HC and 1 FAS. Linear discriminant analysis and support vector machines were also tested, with the latter achieving perfect agreement. Classification was also completed using periorbital, perioral, perinasal, and mid-facial profile patches to determine discrimination capabilities of localized regions. The periorbit and profile patches achieved the greatest agreement. A morph between average HC and FAS profiles captured nasal bridge flattening, mid-facial hypoplasia, philtral smoothing, and retrognathia (Supplemental Movie 3). As expected, the addition of PFAS individuals depressed agreement with clinical categorization because of increased heterogeneity due to relaxing growth and head size criteria (see Table 1). Although face-based classification for HC versus FAS plus PFAS was inferior to that of HC versus FAS, the face profile performed consistently well at 0.91 to 0.93 (Table 4). This concurs with mid-line neurofacial effects found in murine models of ethanol exposure.43,44 Inclusion and exclusion of siblings did not affect classification.
Face Signature Graphs Provide a Panorama of Facial Dysmorphism Across the Fetal Alcohol Spectrum

Figure 4 shows face signatures of 107 alcohol-exposed individuals normalized against HCs: FAS (rows 1 and 2), PFAS (rows 3 and 4), and HE (rows 5–9). As the focus moves from FAS to PFAS to HE, predominant hues change from red-green to green-blue, reflecting greater facial growth and shape difference. Sixteen individuals were omitted due to insufficient controls for normalization. The corresponding signature graph is shown in Fig 5A. Individual signatures offer a panorama of facial dysmorphism across the fetal alcohol spectrum. Graph connectivity links individuals with similar facial dysmorphism (see Fig 5A insets or clusters in Fig 3). Typically, peripheral (resp. central) nodes represent individuals with strong (resp. mild) dysmorphism. Figure 5B is a color-labeled form coding clinical categories: FAS (red), PFAS (blue), and HE (green). Signatures between the upper right of Fig 5A and cluster 8 are almost all labeled HE. Their mainly green-blue hue emphasizes coincidence or expansion compared with controls. In contrast, signatures from the lower left of the graph toward cluster 15 are largely FAS and PFAS (mostly red-green, reflecting contraction or coincidence compared with controls).

Subsets of the HE Group Have Facial Dysmorphism That Is More FAS-like Than HC-like

The second color coding of the signature graph (Fig 5C) shows all FAS and PFAS nodes as red, whereas HE nodes are green circles or squares. Squares highlight 28 HE signatures below clusters with greater FAS or PFAS affinity. This was preserved even when controls were introduced to form a new signature graph (Supplemental Fig 3A). Closer scrutiny of these individuals detected more FAS-like facial features. For example, 6 individuals (Fig 2D) display a flat mid-face and/or flat nasal bridge, as shown by their profile (row 2) and red-yellow regions in heat maps (row 1). In dynamic morphs between them and matched control means, individual 4 through 6 have retrougnathia; and a thin upper lip is suggested in individuals 4 through 6 but not in individuals 1 through 3.

We normalized the HE group against themselves to produce another signature graph (Supplemental Fig 3B) with largely red-green and green-blue face signatures at opposite ends. In the color-coded form (Supplemental Fig 3C), the previously “squared” signatures form a homogeneous aggregate. Thus, they have been selected objectively in 2 signature graphs: first, by FAS/PFAS affinity after normalization against HCs and, second, as a homogeneous subgraph after normalization against HE.

Neurobehavioral Differences in the HE Group Reflect Presence or Absence of FAS-like Facial Features

No differences were found for prenatal alcohol exposure, maternal age, parity, or smoking between the HE subgroup with FAS/PFAS affinity (nonsyndromal heavy exposed with FAS/PFAS-like face signature [HE1]) versus the HE subgroup.
with control affinity (nonsyndromal heavy exposed with more control-like face signature [HE2]) \((P > .10)\). However, HE1 was markedly more affected on neurocognitive measures than HE2, especially for WISC IV Verbal Comprehension IQ and CVLT-C (Table 5). Mean HE1 performance was comparable to FAS, whereas HE2 resembled controls.

**DISCUSSION**

As with genetic syndromes, facial gestalt recognition is a clue to FAS diagnosis. Milder FASD phenotypes and overlapping features in syndromes make recognition challenging. Computer-based facial analysis shows potential for recognizing FAS facial characteristics, but without an accurate test for FASD, studies inducing classification schemes only assess agreement with clinical categorization, which is not standardized. Therefore, comparison of such studies should consider subjects, facial features, and pattern-matching adopted as well as accuracy of agreement.

In a study of a different sample of South African children of mixed ancestry (17 with FAS and 17 controls), clinical categorization considered facial gestalt, growth and head circumference, IQ, behavior and prenatal alcohol exposure. Each face was represented by a set of 3D landmarks and image-based classification used discriminant function analysis. Agreement with clinical categorization involved drop-one-out-testing to produce sensitivity-specificity pairs of 100%:91% at 5 years and 76%:83% at 12 years, suggesting FAS facial dysmorphism becomes less distinct with age.

For a subset of our cohort (36 with FAS and 31 controls) and a Finnish (50 with FAS and 32 controls) cohort, clinical categorization was identical to ours. The 3D face laser scans underwent feature extraction before classification using neural networks. Evaluation involved a 66%:33% training-unseen test set pair, and agreement was calculated at one value of the induced discriminant function. Rather than calculating area under an ROC curve, this selects a single point on it. Discriminant functions were derived for combinations of assessing philtrum smoothness and upper lip thinness by use of a subjective Likert scale or...
objective measures of philtrum luminosity and upper lip circularity. Classification using the Likert scales generated sensitivity-specificity of 100%:100% on the unseen test data at a single value of the discriminant function. Similar results were quoted for discriminant functions derived from all 126 subjects that necessarily involved no unseen testing. This study included individuals from different ethnic backgrounds and controls with different genetic conditions.

Our primary aim was to identify strategies for recognizing facial dysmorphism across the fetal alcohol spectrum. Our ultimate goal is to help pediatricians identify children at high risk for deficits due to prenatal alcohol exposure from different ethnic backgrounds and across wide age ranges. We used pattern matching algorithms and ROC-based analysis of multiple random training-unseen test set pairs to estimate agreement of face classification with a multifaceted diagnostic phenotype (Table 1). Our results showed that DSM-based representation of 3D face shape alone achieved perfect agreement for FAS and good agreement for FAS plus PFAS. Mid-facial profile performed consistently well for both FAS and FAS plus PFAS and will be investigated further in future studies.

We demonstrated that heat map comparisons and dynamic morphing of faces to matched controls revealed facial dysmorphism that was otherwise overlooked. Finally, ignoring clinical categorization, we built graphs linking individuals with similar face signatures. The signature graph using controls for normalization of 107 exposed individuals provided a panorama of facial dysmorphism across the fetal alcohol spectrum. The FAS/PFAS individuals clustered, almost entirely, at

| TABLE 5 Verbal IQ and Learning by FASD Classification |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | FAS             | PFAS            | HE1             | HE2             | HC              |
| **FAS**         | **PFAS**        | **HE1**         | **HE2**         | **HC**          | **t HE1 Versus HE2** |
| Verbal Comprehension Index | 65.4 (13.4) | 63.0 (8.0) | 65.5 (12.9) | 73.3 (10.4) | 73.3 (12.3) | -1.80* |
| CVLT-C         |                 |                 |                 |                 |                 |          |
| List A total correct | 42.7 (12.0) | 41.5 (11.4) | 40.0 (11.1) | 47.3 (9.0) | 45.8 (8.5) | -2.02** |
| Recognition discrimination | 88.5 (11.4) | 88.3 (12.3) | 84.3 (20.1) | 93.7 (6.0) | 93.2 (8.4) | -1.89* |

Values are mean (SD). Standard scores are presented for the WISC-IV; mean number of correct responses is presented for the CVLT-C. HE1, nonsyndromal heavy exposed with FAS/PFAS-like face signature; HE2, nonsyndromal heavy exposed with more control-like face signature.

* n = 9 FAS, 19 PFAS, 15 HE1, 16 HE2, 22 HC.
  b n = 15 FAS, 19 PFAS, 15 HE1, 18 HE2, 38 HC.
  * p < .05.
  ** p < .01.
one end of the graph, with 28 individuals with HE, whereas the remaining individuals with HE clustered at the opposite end. In addition, when individuals with HE were normalized against themselves, the signature graph isolated the same 28 individuals with HE. This HE subgroup showed few of the classic FAS facial features, but flat nasal bridge, malar flattening, philtral smoothing, and micrognathia and retrognathia were revealed in dynamic morphs between the individuals and matched control means.

Different approaches have been advanced for delineating a behavioral profile for alcohol-related neurodevelopmental disorder, but a definitive profile has not yet been identified. It is noteworthy that facial dysmorphism detected in individuals with HE showing closer affinity with the FAS/PFAS aggregation proved to be indicative of neurocognitive deficits approaching 0.5 SD, compared with controls and other children with HE. Signature graph nodes could be color filled at intensities reflecting BMI or by colors reflecting neurobehavior status to investigate links between facial dysmorphism and other biomarkers.

In summary, this study identified novel strategies for detecting facial effects of prenatal alcohol exposure. Heat maps of faces and dynamic morphs to matched controls substantially enhanced the unaided appreciation of facial form. More substantial testing is planned in South Africa, the United States, and the Ukraine. The Collaborative Initiative on Fetal Alcohol Spectrum Disorders plans to make our face visualization tools available to participating dysmorphologists in the coming year. After evaluation and modification, they will be distributed more widely. The 3D cameras are now used routinely by surgeons and orthodontists. Increasingly, there are mobile device apps and websites offering conversion from 2 dimensions to 3 dimensions. Stereo webcams are appearing in laptops for face recognition for security and communication. Thus, 3D face photography is becoming more widely available with the potential to support 3D face shape analysis.

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