

Unique Facial Features Distinguish Fetal Alcohol Syndrome Patients and Controls in Diverse Ethnic Populations

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Background: Effective management of fetal alcohol spectrum disorders (FASD) is dependent on the timely and reliable diagnosis of affected individuals. There are significant diagnostic difficulties because of the reduced prominence of facial features as children age to adulthood as well as potential population or ethnic differences in the most characteristic alcohol-related facial features.

Methods: A total of 276 subjects were recruited from 4 sites (Cape Town, South Africa; Helsinki, Finland; Buffalo, New York; and San Diego, California) and completed a detailed dysmorphology evaluation to classify subjects as either fetal alcohol syndrome (FAS; 43%) or control (57%). Computerized anthropometry was employed to identify facial features that could distinguish FAS patients from controls across a wide age range and across ethnically disparate study populations.

Results: Subjects were placed into 1 of 4 populations based on their ancestry (Cape Coloured, Finnish Caucasian, African American, or North American Caucasian). Analyses performed in each of the 4 study populations were able to identify a unique set of variables which provided excellent discrimination between the 2 groups (FAS, control). In each study group, at least one ocular-related measurement, shortened palpebral fissure, reduced outer canthal width, or reduced inner canthal width, was included in the final classification model.

Conclusions: We found measurements that reflected reduced size of the eye orbit to be a consistent feature discriminating FAS and controls across each study population. However, each population had a unique, though often overlapping, set of variables which discriminated the 2 groups, suggesting important ethnic differences in the presentation of FAS. It is possible that these differences were accentuated by the wide age distribution of the study subjects.

Key Words: Fetal Alcohol Spectrum Disorder, Facial Imaging, Anthropometry, Eye Measurements, Ethnic Differences.

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THE TERM FETAL alcohol spectrum disorders (FASD) defines the adverse effects of alcohol on the developing fetus and represents the entire spectrum of structural anomalies and behavioral and neurocognitive disabilities (Barr and Streissguth, 2001). Individuals at the severe end of the spectrum, with growth deficiency, neurodevelopmental abnormalities or mild microcephaly, as well as a pattern of minor facial anomalies including short palpebral fissures, thin vermilion border of the upper lip, and smooth philtrum are diagnosed with fetal alcohol syndrome (FAS) (Bertrand et al., 2005; Jones et al., 1973). There is a broad continuum of adverse events arising from prenatal alcohol exposure which spans more subtle structural, behavioral or neurocognitive disabilities: these include partial fetal alcohol syndrome (PFAS), alcohol-related birth defects (ARBD), and alcohol-related neurodevelopmental disorder (ARND) (Autti-Ramo et al., 2006; Bertrand et al., 2005; Hoyme et al., 2005).

The most extreme expression of this condition (FAS) is widely recognized in the clinical and public health literature. The prevalence of FAS in the U.S. population has been reported to be 0.5 to 2 per 1,000 live births (May and Gossage, 2001). Fetal alcohol syndrome is even more prevalent in other parts of the world with one of the highest rates in South Africa, 39.2 to 46.4 per 1,000 births (May et al., 2000).

Effective management of individuals with FAS and FASD and their families is dependent on the timely and reliable diagnosis of those who are affected. However, diagnosing FASD among children and adults presents physicians with a challenge, especially when individuals manifest some, but not all, of the clinical features (Astley and Clarren, 2000; Little et al., 1990; Stratton et al., 1996). Adding to the difficulty in diagnosing FASD is that the facial features associated with prenatal alcohol exposure change and become less distinctive as the child grows to adulthood (Streissguth et al., 1991) as well as potential population or ethnic differences in the expression of the facial phenotype (Douglas and Viljoen, 2006).

Previous studies (Moore et al., 2001, 2002) indicated that craniofacial anthropometry, coupled with multivariate analysis can accurately identify individuals with classic manifestations of FAS as well as individuals with less obvious clinical features of the condition. However, traditional anthropometric assessment is time consuming and requires an experienced anthropometrist, or someone with extensive training in anthropometry, to obtain the measurements (Ferrario et al., 1998; Hurwitz et al., 1999).

In clinical settings, craniofacial assessments can be greatly facilitated by noninvasive methods such as computerized anthropometry that can be carried out rapidly on site. Computerized anthropometry uses coordinates of landmarks from surface scans to automatically calculate facial measurements. From an anthropometric and clinical perspective, noncontact 3D-computerized anthropometry offers many advantages over conventional anthropometry. Computerized anthropometry is less time consuming for the patient and examiner, does not require an experienced examiner, allows the quantification of angles, surface areas, and volumes in addition to lin-

ear distances, and provides permanent data that can be used to measure new facial features as knowledge of the craniofacial complex changes (Ferrario et al., 1998, 2005; Hurwitz et al., 1999; Weinberg et al., 2006). These benefits are especially important when working with children or when attempting to characterize a syndrome or disorder across different ages and ethnically diverse populations.

The purpose of this study was to test whether computerized anthropometry can distinguish patients with FAS from controls across a wide age range as well as across ethnically disparate study populations.

METHODS

Participants in this study were recruited as part of an ongoing international consortium, the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) or were recruited previously by the principal investigator for participation in another study. Participants were from 4 sites: Cape Town, South Africa; Helsinki, Finland; Buffalo, New York; and San Diego, California. This study was approved by the Institutional Review Board at each site and at the grantee institutions (Indiana University School of Medicine, Wayne State University School of Medicine, State University of New York at Buffalo School of Medicine and Biomedical Sciences, San Diego State University). All participants and/or their parent(s)/legal guardian(s) provided written informed consent.

As part of the study visit, each participant was examined by 1 or 2 members of the CIFASD Dysmorphology Core, who completed a standardized, uniform assessment as described in Jones et al. (2006). Particular care was taken to exclude patients with a recognizable craniofacial syndrome. A standard classification system, based solely on the basis of structural features (palpebral fissure, philtrum, and vermilion border) and growth deficiency (head size and height and/or weight) consistent with the revised Institute of Medicine criteria, was used to determine preliminary diagnosis. Under this scheme, a participant could receive a preliminary diagnosis of FAS, no FAS, or deferred (Jones et al., 2006). For this study, we designated the individuals given the diagnosis of no FAS as controls. As this designation is not based on prenatal alcohol exposure data, our control sample is not limited to individuals without any prenatal alcohol exposure. Only participants designated as either FAS or control were included in these analyses. Race and ethnicity were reported by the participant or the parent/guardian as part of the study visit. As analyses focused on population differences, only participants reporting themselves to be North American Caucasian (NAC), African American (AA), Finnish Caucasian (FC), or children of mixed ancestry known as Cape Coloured (CC) were included in the analysis.

Collection of 3D Images

Facial images were captured using a commercially available laser scanner, the Minolta Vivid 910fw (Konica Minolta Sensing Americas, Inc., Boulder, CO). The scanner shines a low-intensity "eye safe" laser on the participant. Prior to data collection, a pilot study was completed (by RW and JLR) using a plastic mandible to provide cross calibration assessment of the laser scanners. Preliminary analysis showed that the cameras were comparable with respect to accuracy. Once the inter-scanner variation was found to be minimal, a set of rigorous protocols were established (by JLR) which described in detail how to set up and operate the equipment, scan patients, and postprocess the data. In addition to these written protocols, at least one technician and/or researcher from each collection site completed a 2-day training on the proper use of the scanner and associated software.

Participants were seated approximately 660 mm from the scanner. Natural head posture with a relaxed facial expression was used to

position participants for imaging. This clinically reproducible position allows soft tissue to be scanned in a relaxed state. For each participant, a trained operator located 7 soft tissue landmarks (bilateral: frontotemporale, tragon, gonion; unilateral: gnathion) (Fig. 1) by inspection and/or palpation, and marked them on the cutaneous surface using an eye-liner pencil. Six scans were taken for each participant, including 2 frontal scans and 2 lateral left and right scans with the participant facing near right angles to the scanner. This double redundant approach was utilized to minimize faulty data between frontal and lateral scans caused by participant movement and facial expression. The total scan time for each image was approximately 0.6 seconds. If the participant moved between scans, the procedure was repeated. Collected images were processed using a commercially available software package, Rapidform™ 2004 (INUS Technology Incorporated, Seoul, Korea).

Image Processing and Measurement

Rapidform™, a reverse modeling software package, was used for merging the 3 best lateral and frontal scans into a single 3D model of the participant's face. A trained researcher selected the scans with the best resolution and consistency of patient placement and facial expression. Each 3D facial image was analyzed using a customized software plug-in, written by one of the authors (JLR) using Visual C++ and the Rapidform™ API. An anthropologist (EM, RW) identified 20 landmarks on the 3D model, which the plug-in then used to replicate 16 traditional linear anthropometric facial measurements. The software required double redundant measurement accuracy. This redundant approach required the user to identify at least 2 sets of facial landmarks resulting in <2 mm difference per linear measurement. If the user failed to identify redundant landmarks, she/he was forced to pick a third set or re-pick the existing landmarks until accuracy met the 2-mm specification. Sixteen indirect measurements were collected from each image (Table 1; Fig. 1). For bilateral measurements, only the left side measurements were used. Some participants had missing values for ear length due to hair obscuring the 3D image. When the left ear length was missing, right ear length was used.

Table 1. Craniofacial Measurements and Landmarks

Type	Number	Measurement	Abbreviation
Width	1	Minimal frontal width	ft-ft
	2	Bizygomatic width	zy-zy
	3	Bitragal width	t-t
	4	Bigonial width	go-go
	5	Inner Canthal width	en-en
	6	Outer Canthal width	ex-ex
	7	Palpebral fissure length	en-ex
Depth	8	Upper facial depth	n-t
	9	Midfacial depth	sn-t
	10	Lower facial depth	gn-t
Length	11	Nasal length	n-sn
	12	Nasal bridge length	n-prn
	13	Philtrum length	sn-ls
	14	Lower facial height	sn-gn
	15	Total facial height	n-gn
	16	Ear length	sa-sba

Numbers keyed to Fig. 1.

Previous studies have shown that the most unreliable and least precise measurements are those with small absolute dimensions (Jamison and Ward, 1993; Ward and Jamison, 1991). Therefore, repeated measurements for 2 small anthropometric variables, palpebral fissure length, and philtrum length were reviewed to determine if the measurement error was within an acceptable range. For both variables, 2 measures were computed to evaluate the precision of the measurements. The first was the technical error of measurement (TEM), which provides a measure of the magnitude of error in the original units of measurement. The second was the coefficient of relative variability (CRV), which is computed as the TEM divided by the mean of overall mean of the measurement, and thus reflects the magnitude of the error relative to the size of the measurement. The estimates of TEM in the 4 populations varied from 0.36 to 0.58 across the 2 measures. The estimates of CRV ranged from 0.016 to 0.03. Using the criterion that the TEM should not exceed 5% of the size of the measurement, these data demonstrate a high degree of precision for both palpebral fissure and philtrum length and that the measurement error is within an acceptable range.

Statistical Analysis

Our primary hypothesis was that a unique set of anthropometric features could be identified in each of the 4 study populations (NAC, AA, FC, CC) that discriminated FAS patients from controls. To test this hypothesis, discriminant analysis was performed to identify which combination of age at evaluation and the 16 facial measurements was best able to classify participants as either FAS or control in each of the study populations. To ensure the robustness of the model, both backward and forward stepwise processes, as implemented in SAS (v 9.1.3, Cary, NC), were performed.

Sensitivity is reported as the percent of FAS participants correctly classified and specificity as the percent of control participants correctly classified. The overall correct classification rate is the percent of all correctly classified participants. Results demonstrating the best sensitivity and the best overall correct classification are reported for each study population. Results from discriminant analyses are based on the cross-validation method in which the discriminant function was re-estimated after serially omitting one observation.

RESULTS

A total of 276 images were analyzed of which 18% were NAC, 9% AA, 36% FC, and 37% CC. The majority (54%)

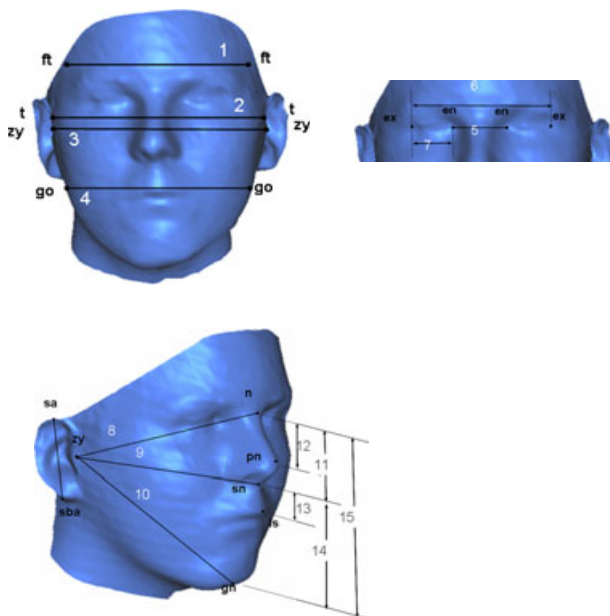


Fig. 1. Anthropometric measurements. The 16 measurements obtained from each of the facial images are shown.

of participants was female, and the age of the participants ranged from 2.75 to 21.17 years. The age of the study participants varied between sites; however, only in the AA sample did the age of the FAS and control patients differ significantly ($p = 0.002$). Therefore, for only the AA data, age-adjusted regression residuals were computed for each measurement and then used in all subsequent analyses. Summary statistics for the 4 population groups are provided in Table 2.

Discriminant analysis was performed separately in each of the 4 study populations (Table 3). The FC sample had the highest overall correct classification rate (93%), based on age and 8 facial measurements: bitragal width, inner canthal width, outer canthal width, palpebral fissure length, midfacial depth, nasal length, nasal bridge length, and ear length (Fig. 1). The discriminant function derived from the CC population correctly classified 92% of the controls and FAS individuals and included in the model age and 5 variables: minimal frontal width, bizygomatic width, inner canthal width, philtrum length, and ear length. The AA population had correct overall classification of 79% of participants, but the function was comprised of only 2 variables, palpebral fissure and philtrum length. The NAC sample had the lowest overall correct classification rate (77%); however, only 2 measurements inner canthal width and outer canthal width were used in classification. Summary statistics for the anthropometric measures in each of the 4 study populations in the 2 study groups are provided in Table 4.

DISCUSSION

In this study, we analyzed the most diverse sample ever reported to identify facial measurements which discriminate FAS participants from controls. We have shown that FAS can be effectively discriminated from controls in Caucasians (FC, NAC), and populations with African admixture (AA and CC). The facial features that most effectively discriminate FAS and controls differed across the populations but in each of the 4 study groups, at least one eye measure, shortened palpebral fissures, reduced outer canthal width, or reduced inner canthal width was included in the model. For all but the CC sample, the eye measurement was either the outer canthal and/or palpebral fissure length. The overall correlation between outer canthal width and palpebral fissure length is 0.79. Thus, when the palpebral fissure is short, the outer canthal distance is also short. However, the overall correlation between inner canthal width and palpebral fissure length is

Table 3. Facial Measurements Used in Final Discriminant Model

Measurements	NAC	AA	FC	CC
Widths				
Minimal frontal width				√-
Bizygomatic width				√-
Bitragal width			√-	
Bigonial width				
Inner canthal width	√-		√-	√-
Outer canthal width	√-		√-	
Palpebral fissure length		√-	√-	
Depths				
Upper facial depth				
Midfacial depth			√-	
Lower facial depth				
Lengths				
Nasal length			√-	
Nasal bridge length			√-	
Philtrum length		√+		√-
Lower facial height				
Total facial height				
Ear length			√-	√-
Sensitivity				
% FAS correct	74	73	96	94
Specificity				
% Control correct	81	85	91	91
% Overall correct	77	79	93	92

NAC, North American Caucasian; AA, African American; FC, Finnish Caucasian; CC, Cape Coloured; FAS, fetal alcohol syndrome.

√ Indicates that this variable used in final classification model for that population; + indicates FAS measurement mean larger than control; - indicates FAS measurement mean smaller than control.

only 0.18 indicating that inner canthal width may be measuring something other than palpebral fissure size. The importance of a reduced outer canthal distance to discriminate FAS and controls supports the results of Moore et al. (2001, 2002) and corresponds with the presence of small head circumferences which are often reported for individuals with FAS.

Palpebral fissure length is one of the key features of FAS. Short palpebral fissures have been associated with an underlying defect in brain development (Braddock et al., 1995). It is assumed that shortened palpebral fissures reflect and result from reduced globe size. Using a mouse model, Parnell et al. (2006) found a direct correlation between palpebral fissure length and globe size. In addition, their findings suggest that shortened palpebral fissure length reflects not only a reduced globe size, but is also indicative of forebrain damage. In spite of ongoing research, the mechanism(s) of prenatal alcohol damage to the developing eye is poorly understood. It is possible that genes involved in neurochemical mechanisms

Table 2. Subject Demographics

	NAC (n = 50)		AA (n = 24)		FC (n = 99)		CC (n = 103)	
	FAS	Control	FAS	Control	FAS	Control	FAS	Control
Number of subjects	19 (38%)	31 (63%)	11 (46%)	13 (54%)	45 (45%)	54 (55%)	49 (48%)	54 (52%)
Number of males	9 (47%)	15 (48%)	4 (36%)	6 (46%)	20 (51%)	19 (49%)	24 (49%)	30 (56%)
Mean age (SD)	10.9 (4.6)	11.1 (2.8)	11.3 (3.8)	6.5 (1.9)	13.1 (3.6)	13.8 (3.6)	5.6 (1.9)	5.3 (2.2)

NAC, North American Caucasian; AA, African American; FC, Finnish Caucasian; CC, Cape Coloured; SD, Standard deviation.

Table 4. Summary Statistics for the Anthropometric Measures From Each of the Four Study Populations

Measurement	NAC				AA				FC				CC			
	FAS Mean	Control SD	FAS Mean	Control SD	FAS Mean	Control SD	FAS Mean	Control SD	FAS Mean	Control SD	FAS Mean	Control SD	FAS Mean	Control SD	FAS Mean	Control SD
Minimal frontal width	97.2	7.5	102.3	7.0	99.4	2.6	98.9	2.0	98.9	5.2	106.8	5.6	88.2	4.0	97.2	5.7
Bizygomatic width	126.5	7.7	132.3	7.0	126.0	2.5	128.9	2.1	128.0	5.8	137.4	7.4	119.1	4.6	122.3	6.7
Bitragal width	128.9	7.5	133.6	6.8	128.2	2.5	131.6	2.0	129.6	6.2	138.6	6.8	121.9	4.9	125.8	6.4
Bigonial width	104.0	9.0	112.7	7.5	105.7	2.7	108.0	2.0	108.7	6.4	117.8	8.9	100.4	5.6	105.3	6.5
Inner canthal width	33.9	2.8	34.4	3.1	34.5	0.6	32.7	0.7	33.2	3.3	34.2	2.4	30.2	2.4	32.2	2.5
Outer canthal width	79.9	4.9	84.8	4.1	80.0	1.7	82.4	1.4	78.6	4.4	84.4	3.8	74.9	4.2	79.0	4.5
Palpebral fissure length	24.3	2.5	26.5	1.7	24.2	0.6	26.1	0.7	23.6	2.0	25.7	1.8	23.7	1.8	24.6	1.8
Upper facial depth	106.5	6.1	111.2	6.4	108.8	1.9	107.4	2.0	107.9	6.5	113.6	4.8	97.5	4.0	100.3	5.3
Midfacial depth	110.9	8.3	115.6	7.3	115.6	2.3	112.0	2.0	113.1	6.9	119.0	5.2	101.3	5.0	104.9	6.1
Lower facial depth	122.5	11.3	129.1	8.5	128.7	3.0	125.1	2.4	127.1	8.0	135.2	7.5	113.2	6.5	118.0	7.9
Nasal length	46.2	3.5	48.2	4.3	46.0	1.2	45.5	1.5	46.3	4.0	49.3	4.0	39.1	3.3	39.1	4.4
Nasal bridge length	39.0	3.9	40.5	4.2	37.0	1.3	36.6	1.1	37.7	4.1	42.0	3.9	31.2	3.2	32.6	3.7
Philtrum length	14.1	1.8	14.5	1.9	16.7	0.6	14.4	0.6	15.6	2.1	16.0	1.9	13.8	2.0	13.7	1.8
Lower facial height	58.1	7.7	58.9	4.8	62.1	1.2	57.3	1.3	58.8	6.2	61.1	5.3	53.2	4.1	53.4	4.6
Total facial height	101.8	9.1	105.0	7.4	104.9	1.6	100.8	2.3	103.0	8.0	108.7	6.8	90.4	6.1	91.0	7.6
Ear length	54.4	4.1	57.2	4.1	52.9	1.1	53.5	1.4	53.3	4.4	57.7	4.0	47.3	4.0	51.1	3.9

NAC, North American Caucasian; AA, African American; FC, Finnish Caucasian; CC, Cape Coloured; FAS, fetal alcohol syndrome; SD, standard deviation.

and alcohol metabolism may play a role (Strömmland and Pinazo-Durán, 2002).

In spite of the cross-ethnic importance of eye measurements as a discriminating variable between FAS and controls, differences were found in the remaining variables which discriminate the 2 groups in each population. There are several possible explanations for the unique set of variables that were found to discriminate FAS and controls in each of the 4 populations. The differing age distributions between the 4 study groups may have contributed to the extensive variation in the type and number of variables needed to distinguish FAS patients from controls. For example, the CC sample had the youngest average age and the narrowest age distribution; whereas the North American sample had the widest age range. Furthermore, the appearance of the FAS phenotype is known to vary with age (Streissguth et al., 1991); therefore, we speculate that some of the differences in our discriminant function results between populations may be attributable to age-related differences in the FAS phenotype.

The differences in results between the populations may also be attributed to variations in the pattern of maternal alcohol consumption. It is well documented that the timing and dose of alcohol exposure has a dramatic affect on the severity of facial involvement (Astley et al., 1999; Earnhart et al., 1987; Sulik, 1984). At the time of analysis, we did not have any information regarding the pattern of maternal drinking. Therefore, it is possible that if maternal drinking pattern was accounted for the variables selected in the model would be more similar.

There are well documented differences in facial structures between ethnic groups (Farkas, 1996; Hajniš, 1972; Hajniš et al., 1989, 1994; Kantero and Tiisala, 1971). In our study, the 2 populations with the lowest rate of overall classification

(AA and NAC) also are arguably the most heterogeneous (various levels of ethnic admixture), whereas the 2 populations with the best classification results are more homogeneous.

Unfortunately, we did not have adequate data to sort out these possible sources of variation. For example, to determine if the discriminating variables change with age *within* a given population, longitudinal data or a broader age range of cross sectional data would need to be collected in each of the study groups to address this issue. To best determine the effect of maternal alcohol consumption, the timing and amount would have to be collected prospectively. It is likely that all 3 factors age, maternal alcohol consumption, and ethnicity play an important role in the resultant phenotype.

One possible limitation of our study is that our control group included children with prenatal alcohol exposure who did not meet criteria for receiving a diagnosis of FAS. Our aim was to compare the effects of age and racial differences on facial features related to FAS, and not the classification of children with prenatal alcohol exposure. Thus, we chose to compare children with a diagnosis of FAS (e.g., those who have the features of interest) to children without this diagnosis, regardless of exposure. While there may be increased variability of our control group, we were successful in identifying facial characteristics that distinguished children with FAS from our control group across study populations, thus meeting our study aim.

When viewed broadly, our findings are consistent with clinical descriptions which focus on the orbital region (palpebral fissure size) and midface (midfacial hypoplasia and thin lips with flat philtrum) as the discriminating features in FAS. Our results are also consistent with previous anthropometric studies which report that individuals with FAS generally have smaller faces in all dimensions, compared

with age-matched controls (Moore et al., 2001, 2002). A recent cephalometric study (Naidoo et al., 2006) of a sample of CC children (FAS and controls) suggests that generalized microsomia is also reflected in the underlying skeletal structure. Thus, individuals with prenatal alcohol exposure appear to have a general reduction in most skeletal dimensions, including those in the cranial base and midfacial depths.

The effective management of FASD requires early detection and diagnosis. This study evaluated the possibility of using computerized anthropometry to distinguish patients with FAS from controls across a wide age range as well as across ethnically disparate study populations. We have demonstrated that a unique set of facial measurements can be obtained from remotely gathered 3-dimensional images and used to separate FAS from control individuals in each population we studied. The effectiveness of this quantitative approach matches that of pediatricians trained by dysmorphologists to recognize FAS individuals (Jones et al., 2006) and suggests that the use of a noninvasive, objective method to identify individuals with FAS could lead to earlier and more efficient identification of children in need of early intervention. However, these individuals are at the extreme in the continuum of facial measurements. Therefore, the most immediate benefit of the use of remote imaging will be the collection of large samples of alcohol-exposed individuals from which further clarification of the facial dysmorphology associated with FASD will be possible. Such analysis in combination with similar work from animal models will help us understand the embryological relationship between brain structure, facial morphology, and the dose and timing of ethanol exposure.

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