



Published in final edited form as:

J Dev Behav Pediatr. 2010 May ; 31(4): 304–316. doi:10.1097/DBP.0b013e3181dae243.

Population Differences in Dysmorphic Features Among Children With Fetal Alcohol Spectrum Disorders

Philip A. May, PhD^{*}, J. Phillip Gossage, PhD^{*}, Matthew Smith, MD[†], Barbara G. Tabachnick, PhD[‡], Luther K. Robinson, MD[§], Melanie Manning, MD^{||}, Mauro Cecanti, MD[¶], Kenneth Lyons Jones, MD^{**}, Nathaniel Khaole, MD^{††}, David Buckley, MA^{*}, Wendy O. Kalberg, MA, CED^{*}, Phyllis M. Trujillo, MA^{*}, and H. Eugene Hoyme, MD^{‡‡}

^{*}Center on Alcoholism, Substance Abuse, and Addictions (CASAA), The University of New Mexico, Albuquerque, NM

[†]Department of Pathology, University of Pittsburgh, School of Medicine, Pittsburgh, PA

[‡]University of California, Northridge, CA

[§]Department of Pediatrics, School of Medicine, State University of New York, Buffalo, NY

^{||}Department of Pediatrics, School of Medicine, Stanford University, Stanford, CA

[¶]University of Rome, La Sapienza, School of Medicine, Rome, Italy

^{**}Department of Pediatrics, School of Medicine, The University of California, San Diego, San Diego, CA

^{††}Minister of Maternal Health and Genetics, Republic of South Africa

^{‡‡}Department of Pediatrics, Sanford School of Medicine, The University of South Dakota, Sioux Falls, SD

Abstract

Objective—To examine the variation in significant dysmorphic features in children from 3 different populations with the most dysmorphic forms of fetal alcohol spectrum disorders, fetal alcohol syndrome (FAS), and partial fetal alcohol syndrome (PFAS).

Method—Advanced multiple regression techniques are used to determine the discriminating physical features in the diagnosis of FAS and PFAS among children from Northern Plains Indian communities, South Africa, and Italy.

Results—Within the range of physical features used to identify children with fetal alcohol spectrum disorders, specifically FAS and PFAS, there is some significant variation in salient diagnostic features from one population to the next. Intraclass correlations in diagnostic features between these 3 populations is 0.20, indicating that about 20% of the variability in dysmorphology core features is associated with location and, therefore, specific racial/ethnic population. The highly significant diagnostic indicators present in each population are identified for the full

samples of FAS, PFAS, and normals and also among children with FAS only. A multilevel model for these populations combined indicates that these variables predict dysmorphology unambiguously: small palpebral fissures, narrow vermillion, smooth philtrum, flat nasal bridge, and fifth finger clinodactyly. Long philtrum varies substantially as a predictor in the 3 populations. Predictors not significantly related to fetal alcohol spectrum disorders dysmorphology across the 3 populations are centile of height (except in Italy) strabismus, interpupillary distance, intercanthal distance, and heart murmurs.

Conclusion—The dysmorphology associated with FAS and PFAS vary across populations, yet a particular array of common features occurs in each population, which permits a consistent diagnosis across populations.

Index terms

fetal alcohol spectrum disorders (FASD); fetal alcohol syndrome (FAS); partial fetal alcohol syndrome (PFAS); dysmorphology; human malformations

The availability and regular use of a variety of alcoholic beverages by substantial proportions of many populations make alcohol one of the most prevalent teratogens, if not the most prevalent. Commonly cited prevalence estimates are that cases of fetal alcohol syndrome (FAS) range from 0.5 to 3.0 per 1000 births in the United States.^{1–3} But more recent estimates are higher at 2 to 7 per 1,000 children.⁴ Fetal alcohol spectrum disorders (FASD) have been frequently cited as affecting 1% of all children in the United States,⁵ but recent estimates based on in-school studies in the United States and Europe range from 2% to 5%.⁴ While many doubt that their communities have cases of severe FASD, FAS has been identified in all racial and ethnic groups^{2,6} and, recent studies in public schools of Italy⁷ and in the United States^{4,8} have identified a substantial number of cases of FAS and other FASD. Indeed, prenatal exposure to alcohol may be the most common cause of mental retardation in the United States and other parts of the world.^{1,5,9}

The term FAS was coined by Jones and Smith¹⁰ to encompass the features of children adversely affected by in utero exposure to alcohol. Even though some of the clinical features of alcohol-exposed children had been described before,^{11–13} the work of Jones and Smith laid the foundation for identifying alcohol as the cause of this pattern of anomalies and catalogued the multiple features that characterize the syndrome. The diagnoses of FAS and other FASD are being refined as investigators further elucidate and clarify the major continuum of effects resulting from prenatal alcohol exposure.^{14,15} This effort is vital to strengthen the diagnostic methods for identifying FASD and to increase the screening for children with an FASD, as most are currently undiagnosed and untreated.

Major morphological features of FAS include microcephaly, a hypoplastic midface, which includes a smooth philtrum, a thin upper lip, and changes in the length of the philtrum. The size of the eye and the orbits are affected, including the palpebral fissures, which are shorter than normal. Unfortunately, there is considerable overlap in dysmorphology with other syndromes and teratogenic exposures. Therefore, a diagnosis must include additional physical, clinical findings. Additional findings currently in use in the refinement of an FAS diagnosis include the shape and volume of the vermillion border of the upper lip and the

philtral columns, the neurobehavioral phenotype, and documentation of the pattern and amount of maternal drinking and other associated risk factors.^{1,14–17} Only by gathering data on multiple variables over several domains of assessment are investigators better able to clarify the degree to which a child is affected by prenatal alcohol exposure.

Although progress has been made, there is still debate about the degree of changes in normal morphology necessary to warrant a diagnosis of FAS,¹⁸ and maternal risk factor studies and specific studies of the characteristic diagnostic criteria for various levels of FASD are advancing the field.^{14,15} Recent work catalogues and elaborates on the array of child physical features associated with prenatal alcohol abuse in several populations,^{7,19–21} and the amounts of alcohol and patterns of consumption necessary to affect children cognitively and behaviorally are being identified.^{22–29} One of the difficulties in diagnosing FAS is the substantial variability of the effects of alcohol from one individual to the next and a broad spectrum of presentations. This diagnostic challenge lead to the term FASD.^{30,31}

The Spectrum of Diagnoses Within Fetal Alcohol Spectrum Disorders

FASD is a categorical term. The Institute of Medicine defined the spectrum into 4 diagnoses. From the most growth deficient, dysmorphic, and generally most cognitively impaired to the least the diagnostics categories are FAS, partial FAS (PFAS), alcohol-related neurobehavioral disorders, and alcohol-related birth defects. Children with PFAS have many of the facial and limb dysmorphia as do children with FAS, but they are less growth retarded and not always as affected cognitively. Children with alcohol-related neurobehavioral disorders have substantially less dysmorphic features but suffer measurable cognitive impairments and a behavioral phenotype similar to children with FAS and PFAS. Also children with alcohol-related birth defects have some major alcohol-linked physical/ anatomical markers, but their cognitive-behavioral profile falls into the normal range.^{1,15}

Prevalence and Characteristics of Fetal Alcohol Spectrum Disorders Varies Substantially by Population

Several methods are used to screen for FASD including passive surveillance, clinic-based studies, and active case ascertainment studies.³ Each method has strengths and limitations; however, ongoing research in schools and special referral clinics using active case ascertainment methods has been successful in locating and documenting many cases of FASD in general populations.⁴ Some past active case ascertainment studies have identified moderate to high FAS rates 1.0 to 8.97, and 120 per 1000 children^{32,33} among some groups of American Indians, high rates among the South African Colored population, 51.3 to 67.2 per 1000 children,^{21,34} and rates of 3.7 to 7.4 per 1000 children in Italy.⁷ Rates of FAS and PFAS combined are also variable and high with 2 to 5 times as many cases of PFAS as FAS in developed countries, and the percentages of FASD ranging from 2% to 5% in some studies.^{7,21,33,35,36} Active case ascertainment methods have not only revealed groups with high rates of FASD but also may lead to further clarification of the prevalence somewhat variable traits of both FAS and other FASD in general populations. FASD may occur more frequently than previously estimated from studies in tertiary clinics where usually only the classic, most dysmorphic, and affected children are seen.

Original comparisons of the offspring of Plains Indian women and the women of a South African community revealed wide variation in the effects of prenatal alcohol exposure on children.³⁷ Alcohol seemed to have a differential effect on the children born in one group over the other, and the specific nature of the dysmorphology varied between racial groups. Common variables contributing to variation in risk for FASD included the quantity, frequency, and timing of drinking during the index pregnancy, maternal age at pregnancy, gravidity, parity, maternal weight and body mass index, and lifelong and current nutrition. Binge drinking women who were older, had been pregnant and given birth more, and had poor nutrition and low body mass index were the most likely to bear highly dysmorphic FASD children. Comparing results from the above two populations demonstrated the importance and difficulty in interpreting maternal, physical, environmental, and genetic influences on the nature of FASD in children, and it underscored the need to compare the dysmorphology of FASD both with normals within groups and also the commonalities between groups.

In this article, we use data from active case ascertainment studies of 3 distinct populations of children to better clarify the similarities and differences in dysmorphology, growth, and unique physical features. The data illuminate the importance of different morphological features within and between these populations and are useful for defining differences in the clinical features of FASD found in general populations as opposed to the more severe features identified in studies from referral clinics.²

METHODS

Sampling Methods and Samples

The Northern Plains American Indian data come from a National Institute on Alcohol Abuse and Alcoholism-funded epidemiologic study, which used active case ascertainment through outreach to identify cases of fetal alcohol spectrum disorders (FASD) in entire communities.^{1,3,38} Physicians, teachers, and other representatives were taught to recognize common traits of FASD and refer children to special clinics for diagnosing FASD and similar disorders of either a teratogenic or genetic origin. An interdisciplinary team examined each child for the morphological characteristics of FASD and other birth defects, IQ, and neuropsychologic traits. Mothers were also interviewed about childbearing, maternal risks, and consumption of alcohol. In addition, a sample of unaffected children matched for age, sex, and community of residence was collected for comparison (controls). The mothers of the control children were also interviewed and evaluated in the same manner, and they became the maternal controls. The total sample for the Plains group is 321 children, 98 of whom are cases of fetal alcohol syndrome (FAS) (n = 49) or partial FAS (PFAS) (n = 49). Because of the residence pattern in these communities, the ethnic composition of this sample is 91.2% American Indian, 7.5% white, 0.8% Hispanic, and 0.4% Black/African-American.

The South African and Italian data are derived from studies using active case ascertainment methods in a two-tiered, diagnostic process among all first grade children in multiple elementary schools.^{7,21,19,34} Height, weight, and occipitofrontal (head) circumference were assessed in the first tier. If a child's measurements were 10th centile on occipitofrontal (head) circumference or height or weight, or if referred by a teacher for learning or

behavioral problems, he/she was referred to the second tier consisting of a complete physical examination and morphology assessment by at least 2 pediatric dysmorphologists, each blinded to the background, history, and reason for the examination. Controls were randomly selected from the same classroom.

Three South African studies were funded by National Institute on Alcohol Abuse and Alcoholism and the National Institute on Minority Health and Disparities. After parental permission, all children with consent participated (99-81% in each wave) in a 2 tier, active case ascertainment screening process. The evaluation included assessing physical growth, dysmorphology, cognitive and behavioral development, and interview assessment of maternal risk factors including alcohol consumption.²¹ Controls without FASD were selected using random methods. The sample presented here (n = 300) is from the third wave of screening performed in 2002. There are 73 children with FAS (n = 55) or PFAS (n = 18), and the remainder of the sample are controls. The ethnic composition of the South African sample is 94.4% Colored, a group of people who make up the majority of the population of the Western Cape Province. Colored represent a rich admixture of African (mainly of Koi-San tribal groups) European, East Indian, and Malaysian origins. The rest of the sample is 4.3% Black-African, and 1.3% white.

The Italian study was funded by National Institute on Alcohol Abuse and Alcoholism and the Health Department of the Lazio regional government. Randomly selected primary schools (n = 43) in 2 health districts of the Lazio region were recruited. Two tier screening identical to that in South African studies was performed in Italian schools with approval from Italian and US institutional review boards.⁷ The total sample is 300 children who were assessed in 2005–2007. Forty-eight of the children are cases of FASD (8 FAS, 36 PFAS) and 256 are randomly selected controls. The Italian sample is 98.7% white (mostly Italian native), 0.8% Black, and 0.5% Asian.

Institute of Medicine Categories and Criteria for Fetal Alcohol Spectrum Disorders

In each of the samples, the diagnostic components and guidelines of the revised U.S. Institute of Medicine^{1,15} were used to assess specific FASD. The Institute of Medicine diagnoses describe the full continuum of FASD from most dysmorphic and generally severely affected in cognitive and executive functioning to the less obvious, less dysmorphic, and usually less severe manifestations: fetal alcohol syndrome (FAS), partial FAS (PFAS), alcohol-related neurobehavioral disorders (ARND), and alcohol-related birth defects (ARBD).^{1,15} FAS and PFAS, are currently the most readily recognized by knowledgeable clinicians. Furthermore, for most in-school studies to date, these are the two most common manifestations diagnosed.^{7,19–21}

For the diagnosis of FAS a child must have (1) evidence of a characteristic pattern of minor facial anomalies including at least 2 or more of the key facial features of FAS (palpebral fissures 10th centile, thin vermilion border, or smooth philtrum), (2) evidence of prenatal and/or postnatal growth retardation (height or weight 10th centile), (3) evidence of deficient brain growth (structural brain anomalies or occipitofrontal [head] circumference 10th centile), and if possible, (4) confirmation of maternal alcohol consumption directly from the mother or a knowledgeable collateral source. For a diagnosis of partial FAS

(PFAS), a child must have (1) evidence of a characteristic pattern of facial anomalies including 2 or more of the 3 mentioned above, (2) one or more other characteristics, such as prenatal or postnatal growth retardation (< 10th centile) in height or weight), (3) small occipitofrontal [head] circumference (< 10th centile), and/or evidence of a complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level and unexplainable by genetic composition, family background, or environment alone, and if possible, (4) confirmation of maternal alcohol consumption directly from the mother or a collateral source.¹⁵ The most common difference between FAS and PFAS is that children with PFAS are generally not growth retarded.

The diagnoses of alcohol-related neurodevelopmental disorder (ARND) and ARBD are not used in this article, because the limited number of these diagnoses provided in these studies was not included in the analyses presented in this article. ARBD and ARND are not as dependent on dysmorphology and because the methods used in these studies rely heavily on indicators of deficient growth and dysmorphology for inclusion, these methods do not detect all cases of ARND and ARBD (e.g., a representative population sample of ARND/ARBD).

Intellectual and Behavioral Assessment

The diagnostic process for each child in Tier II of the screening at each site also included developmental tests that measured both intellectual development and behavioral problems often associated with FASD. Similar psychological and behavioral testing was completed for each child, both subject and control. Although using somewhat different tests and different languages with each of the 3 populations, similar domains of intellectual functioning and behavioral traits were assessed in each population.

Controls

The control children in the South African and Italian in-school studies were selected by random selection from a list of all children enrolled. For the referral study in the Plains, controls represent a convenience sample of children from the same reservation communities. All control children underwent the same examinations and testing as the FASD cases and were found to be normal. Mothers of the control children were the maternal controls.

Maternal Interviews

Similar, structured interviews were performed with mothers of both control and affected children in each of the 3 populations. These interviews collected maternal risk data including childbearing, demographic and socioeconomic measures, health status, social variables, and alcohol use (by quantity, frequency, and timing) and other substance use by similar timeline follow back methods.^{7,21,39–42}

Case Conferences for Final Diagnoses

All of the individual examinations, assessments, and interviews were performed by investigators from various disciplines, each blinded to the child's history, background, findings of other examiners, and reason for examination. Once the data were collected, interdisciplinary case conferences were held for a final diagnosis where data from each of

the domains are presented by an examiner from that domain, ((a) physical growth, physical development, and dysmorphology, (b) intellectual and behavioral, and (c) maternal risk factors), and pictures of each child are reviewed, discussed, and final diagnosis is made by the group.

All physical growth and dysmorphology features observed and measured in a child's examination are recorded on a standardized and weighted checklist.¹⁵ Possible dysmorphology scores range from 0 to 35. A high dysmorphology score and specific, key features of FASD (as described in the diagnostic section)¹⁵ must be present for a positive diagnosis of FAS or PFAS. Mean total dysmorphology scores for cases and controls in each population are found in Table 1. Furthermore, for any of the FASD diagnoses to be made, other known birth defects and patterns of disabilities must be ruled out, (e.g., Williams, Down, de Lange, and fragile X syndromes).

Data Analysis

Analysis of the data was performed by first comparing cases to controls and significance was evaluated with a Bonferroni-adjusted alpha level of .0015 with *t*-tests and one way analysis of variance. Descriptive data analysis was performed using EPI Info software,⁴³ and comparative and regression were performed using the SPSS software.⁴⁴ To adjust for multiple comparisons, the alpha level in the logistic regression tables was set at 0.0015 for individual comparisons.

Regression Analyses—Specific Considerations

The preliminary analyses consisted of two sets of three separate sequential regressions for data from the Plains, Italy, and South Africa. In each, 18 physical characteristics were sequentially entered into a regression equation to predict dysmorphology. The dependent variable, dysmorphology, showed substantial departure from normality in all data sets, violating an assumption of parametric statistical analysis. Therefore, a square root transformation was applied in all parametric analyses. A significant difference among transformed (square root) means corresponds to a significant difference among group medians.

Predictors, in order of entry into the equation, were height, weight, head circumference, palpebral fissure length, narrow vermilion, smooth philtrum, long philtrum, strabismus, interpupillary distance, ptosis, intercanthal distance, nasal bridge, anteverted nostrils, aberrant palm crease, fifth finger clinodactyly, camptodactyly, heart murmur, and railroad ears. Several predictors were converted to age- and sex-adjusted centiles: height, weight, head circumference, interpupillary distance, and intercanthal distance.

The first set of analyses used the entire sample of children from each site. The second set omitted children diagnosed as PFAS. A two-level hierarchical model then assessed the effects of the predictors over the three locations. First level units were children and second level units were locations. Hierarchical models are those in which data collected at different levels of analyses (e.g., children and locations) may be studied without violating assumptions of independence in linear regression. For example, the fact that different physicians test children in different environments means that responses from children within

each location are not independent of one another. Multilevel modeling takes account of these dependencies by estimating variance associated with group (e.g., location), differences in average response (intercepts), and group differences in associations (slopes) between predictors and outcomes (e.g., location differences in the relationship between narrow vermillion and square root of dysmorphology). This is accomplished by declaring intercepts and slopes to be random effects. Thus, fixed effects are average slopes over all locations and random effects are group difference in average dysmorphology and in relationships between dysmorphology and each predictor.

The 3 data sets varied in the amount of missing data. The South African data set had no missing values. Two cases were omitted from the Italy data set because of missing values for one or more predictors. Because most of the Italian children did not have measurements for interpupillary distance, that variable was omitted from the analyses of Italy data. For the Plains Indian data set, 21% of the cases had missing values for interpupillary distance, with lesser amounts of missing values for four other predictors. SPSS MVA was used to impute a complete data set using the EM algorithm, after omitting the 2 cases with missing values on dysmorphology.

Multivariate outliers ($p < .001$) were numerous in all the data sets. However, these outliers were caused by extremely uneven splits in some of the dichotomous predictors, which were not amenable to transformation. For example, only about 3% of the cases showed strabismus, possibly distorting standard errors in analyses that include that variable. Therefore, the decision was made to set a criterion of $p < .0015$ for tests of individual predictors to compensate for underestimation of standard errors as well as inflated familywise Type I error rate.

RESULTS

Table 1 introduces the data of interest. First, the data are grouped by study population: Plains Indians, Italians, and South Africans. Then within each study sample, the data are grouped by child's final diagnosis: fetal alcohol spectrum disorders (FASD) (either fetal alcohol syndrome [FAS] or partial FAS [PFAS]), or not FASD.¹⁵ Forty-six sets of analyses are reported in Table 1; of those, 31 are statistically significant at the standard alpha of .05, but 26 are significant when the adjusted multiple comparison level of .0015 is applied.

Overall, sixty-four percent of the mothers reported consuming alcohol during the index pregnancy; more mothers of children with FASD reported drinking than did control mothers (84 vs. 44%) and at higher levels. (For specific levels see Viljoen et al⁴⁵ and May, et al).^{7,19,46} Plains Indian mothers who had given birth to an FASD child consumed an average of 7.6 (± 6.27) drinks on a typical drinking day, which was substantially more on average than reported by similar Italian (0.4 ± 0.6) or South African (4.2 ± 4.1) mothers. Binge drinking (defined as 3 or more drinks per occasion) was more prevalent among Plains Indian and South African mothers. The subjective assessments of the Italian interviewers, all of whom were highly experienced alcohol abuse counselors, indicated that there was likely significant underreporting of alcohol use in the Italian sample.

The majority of South African children (Table 1) are small, with low centile scores on the National Center for Health Statistics (NCHS) growth charts for height, weight, head circumference, and palpebral fissure length. As shown in the rest of Table 1, other features consistent with an FAS or PFAS diagnosis are observed in all 3 populations. More detail in descriptive data on both the children and the mothers in the individual populations is found in other publications.^{7,19,21,34,37,45,46}

Sequential Regression Analyses of Full Sample and Excluding PFAS for Each Population

Table 2 shows results of sequential regression analyses using the full sample of FASD children (including PFAS) and controls for the 3 populations. Table 3 shows the results of regression analyses for the reduced sample of FAS children (omitting PFAS) and controls for the 3 populations. Tables 2 and 3 include regression coefficients (B) and their standard errors, beta weights (β), indicating the contribution of each predictor after adjusting for all other predictors, and incremental squared semi-partial correlations (sr^2), showing the contribution of each predictor as it enters the prediction equation in sequential order.

Plains Indians

Among Plains Indians, the set of 18 variables significantly predicts the square root of dysmorphology in the whole data set, $F_{(18,302)} = 99.54$, $p < .001$, adjusted $R^2 = 0.85$ with 95% confidence interval (CI) from 0.81 to 0.87. The last column of the left portion of Table 2 shows that 12 of the variables predict square root of dysmorphology at the point at which they enter the sequential model. These include centiles for the common size measurements (height, weight, and head circumference), palpebral fissure length (PFL), vermilion and philtrum measurements, nasal bridge, anteverted nostrils, aberrant palm crease, camptodactyly, and “railroad ears.” Looking at each predictor in the context of the entire data set (column 2), however, the centiles of common size measurements no longer significantly predict dysmorphology after adjustment for other predictors because of their correlations among all predictors.

Table 3 shows the results of the statistically significant prediction of square root of dysmorphology for the Plains sample without partial FAS for the set of 18 variables, $F_{(18,253)} = 84.51$, $p < .001$, adjusted $R^2 = 0.85$ with 95% CI from 0.80 to 0.87. Ten of the variables predict square root of dysmorphology at the point they enter the sequential model. These 10 also were significant predictors for the entire sample; however, camptodactyly and “railroad ears” no longer add to prediction after adjusting for higher priority variables. Eight of these 10 predictors also contribute to prediction after adjustment for all other variables; height and head circumference centiles do not contribute to prediction after adjustment for all other variables.

Italian Sample

In Italy, measurements of interpupillary distance were made on only a small portion of the sample (79 of 302 cases). Therefore, that predictor was omitted from the analysis. The remaining set of 17 variables significantly predicts the square root of dysmorphology, $F_{(17,282)} = 60.01$, $p < .001$, adjusted $R^2 = 0.77$ with 95% CI from 0.70 to 0.80. The last column of the middle portion of Table 2 shows that 10 of the variables predict square root of

dysmorphology at the point at which they enter the sequential model. These include centiles for the common size measurements (height, weight, and head circumference), PFL, vermillion and philtrum measurements, anteverted nostrils, aberrant palm crease, and fifth finger clinodactyly. Again, the common size measurements no longer predict square root of dysmorphology once adjusted for the entire set of predictors. In this analysis, PFL also fails to predict dysmorphology after adjusting for other predictors.

For the Italy sample, excluding partial FAS children in the middle portion of Table 3, the 17 variables (exclusive of interpupillary distance) significantly predict square root of dysmorphology, $F_{(17,246)} = 43.47, p < .001$, adjusted $R^2 = 0.73$ with 95% CI from 0.65 to 0.77. Eleven of the variables were significant predictors at the point at which they enter the sequential model, as seen in Table 3 (last column). These are the same as for the entire sample of children, with the addition of camptodactyly when partial FAS children are excluded. Ten of these 11 predictors remain significant after adjustment for all other variables. Height and weight are significant predictors when entering the model early but no longer contribute once all other variables are taken into account.

South African Sample

For the South African data, the set of 18 variables also significantly predicts the square root of dysmorphology, $F_{(18,226)} = 87.79, p < .001$, adjusted $R^2 = 0.87$ with 95% CI from 0.82 to 0.89. The last column of Table 2 shows that 11 of the variables predict square root of dysmorphology at the point at which they enter the sequential model. These include centiles for the common size measurements (height, weight, and head circumference), PFL, vermillion and philtrum measurements, ptosis, aberrant palm crease, and fifth finger clinodactyly. All these except centile of height continue to predict square root of dysmorphology even after adjustment for all other variables.

For the South African sample without partial FAS, the results produce $F_{(18,208)} = 77.17, p < .001$, adjusted $R^2 = 0.86$ with 95% CI from 0.81 to 0.88. Twelve of the variables significantly predict the square root of dysmorphology at the point at which they enter the sequential model. One of these, camptodactyly was not a significant predictor when the sample included partial FAS children. All these predictors, except height, continued to contribute to the model prediction even after adjustment for all the other variables, as seen in the Table 3 (last column).

Multilevel Model

Attempts at imputing data for interpupillary distance for the Italian sample were unsuccessful. Therefore, two varieties of model were analyzed through Hierarchical Linear Modeling (HLM) 6.04 using full maximum likelihood estimation. One set of models included data from all 868 cases on 17 of the predictors, omitting interpupillary distance. A second set of models looked at all 18 predictors but included only those 79 cases from Italy with complete data. The 17-predictor models were chosen for reporting because interpupillary distance showed neither a relationship with dysmorphology nor a difference among locations in the relationships with dysmorphology in the 18-predictor model (nor in

any of the sequential regression analyses). Children with partial FAS were included in this analysis.

The intercepts-only model indicated statistically significant variance among locations, $\chi^2(2, N = 868) = 201.56, p < .002$, with an intraclass correlation of 0.20, indicating that about 20% of the variability in dysmorphology scores is associated with location. Thus, the locations differ significantly in mean dysmorphology variables within the standard array of features associated with the diagnoses of FASD in any human group. A significant difference among transformed (square root) means (intercepts) corresponds to a significant difference among medians for the three groups. Thus, South African children on average have higher dysmorphology scores (median = 12.0) than those of Plains Indian (median = 4.5) or the Italian children (median = 6.0).

A full model that included random, as well as fixed effects for the 17 predictors, was significantly better than one in which only the intercepts (mean differences in square root of dysmorphology among locations) were included, $\chi^2(187, N = 868) = 1565.61, p < .001$. Interactions between intercepts and slopes and interactions among slopes as random effects are not interpreted because they were not hypothesized, or are they of interest, although HLM 6.04 includes all of them in estimating the multilevel model.

Tables 4 and 5 provide the results of the multilevel model. Table 4 indicates that 5 measures significantly predict square root of dysmorphology unambiguously when data are combined across all 3 locations and adjusted for random effects (i.e., interactions between locations and effects of predictors): small PFL, narrow vermilion, smooth philtrum (flat), nasal bridge, and fifth finger clinodactyly. Additionally, Table 5 indicates that long philtrum has a significantly different relationship with dysmorphology for the 3 locations (i.e., an interaction between locations and effects).

Comparing results with those of the sequential regression analyses of the full samples, Table 2 shows that although long philtrum is positively related to square root of dysmorphology in all 3 samples, the relationship is stronger among the Plains Indian ($B = 0.77, sr^2 = 0.09$) and Italian children ($B = 0.61, sr^2 = 0.09$) than among the South African children ($B = 0.34, sr^2 = 0.04$). Because of the diminished power of analyses of fixed effects when all of them are adjusted for random effects (and all random effects are adjusted for fixed effects), some of the variables that showed statistically significant predictability in 1 or 2 of the locations, when tested separately, fail the test when combined over locations. Thus, the results of the multilevel model are the most conservative of all the analyses. Predictors that were not significantly related to dysmorphology in any of the analyses (Tables 2 and 3) are strabismus, interpupillary distance, intercanthal distance, and heart murmur.

DISCUSSION

There are limitations to be noted in this study. Although the samples may be considered small for this type of analysis, they represent some of the largest samples of reliably diagnosed children with fetal alcohol spectrum disorders (FASD) from any race or ethnicity and normal controls anywhere. Furthermore, samples were collected from active case

ascertainment in entire communities and therefore are more representative of their general populations than samples collected from fixed clinics, especially tertiary clinics. Second, although 2 of these samples were drawn from active screening in representative public schools, 1 sample consisted of active ascertainment referrals to tertiary diagnostic clinics. To account for selectivity in the later method, the same outreach and referral system was implemented in 7 communities, which should have resulted in variable patterns of over and under referral, possibly balancing selectivity across sites. Furthermore, similar referral patterns of selectivity may have been introduced by similar consent processes used in each method of case selection (in-school and referral). Finally, although missing data were minimal, where these existed, full data sets were imputed using standard algorithms.

Although each of the included studies was performed independently, this article is one of the first attempts to compare FASD diagnostic findings across general populations. As is commonly acknowledged, when an extensive catalogue of the features of fetal alcohol syndrome and partial FAS are considered, some variables consistently predict across populations whereas others vary in their predictive value from population to population. But when total dysmorphic features are considered in case control comparison within each population, the summation of positive and significant findings are predictive of an FASD. Data show that this approach holds true among different ethnicities, in the face of variations in prevalence of significant dysmorphic findings among controls.

Other interesting findings are revealed when comparing other FASD traits in addition to the common physical size variables (e.g., height and weight). The South African controls have higher percentages of narrow vermilion border, smooth philtrum, short interpupillary distance, flat nasal bridge, and anteverted nostrils. Meanwhile, Plains Indian controls have higher percentages of “railroad track” ears, likely a normal genetic variant among this population. Italian controls, however, fall between the 2 groups in most categories with the exception of philtrum length and strabismus. These findings suggest inherent differences in morphology that make it necessary for clinicians to be cautious when suggesting a diagnosis of FASD with few dysmorphic traits, the need for awareness of normal genetic traits in a population, and for researchers to use controls from the same population.

The sequential regression analyses for each ethnic group reveal variation in the utility and importance of the common size measurements. Plains Indian children showed that height, weight, and head circumference have less value for predicting FASD diagnoses. Similarly, in Italian (white) children, height, weight, and head circumference are less important in predicting FASD; however, palbebral fissure length, a commonly cited finding in FASD, also held less value. This suggests that the diminished value of the common size measurements is related to their syndromal relationship with the individual dysmorphic variables.

In the South African (Colored) children, weight, head circumference, and palbebral fissure length remain important predictors of FASD. We believe that the effect of under nutrition is a major reason that these measurements retain their importance among South African children, while being less important in the other populations. However, this finding is important in the clinical setting in all populations. Many clinicians use height, weight, and

head circumference centiles to quickly assess whether children may be afflicted with a developmental defect. In Plains Indian and Italian children, these findings, although suggestive of FASD, seem to have less value for diagnosing children with fetal alcohol syndrome and partial FAS and indicate the need to place more emphasis on the other findings. Meanwhile, in South African children, focusing on common size measurements may hold more importance for an FASD diagnosis, but abnormal (dysmorphology) findings are also more common in South Africa. The growth data in South Africa may make the case for growth charts specific to the South African Colored population, but the current standard charts adopted in the Republic of South Africa are the same as the U.S. (NCHS) charts.

Although the predictive value of height, weight, and head circumference varies between groups, all the children with FASD show substantial relative deficits in these traits in their respective populations. The extreme difference in both controls and FASD children between the South African children and the other groups is clearly related to nutrition.^{21,34,46} Previous analyses of the South African study revealed that a mother's nutritional status and low body mass index values were important in predicting FASD. The findings of these regression analyses, coupled with previous analysis and the extremely high rate of FASD in the South African community,^{21,46} reinforce that nutritional status may play a large role in development of FASD and severity of the dysmorphology.

Previous work indicated that FASD rates were much higher in the South African study community³⁷ when compared with Plains Indians. Interestingly, some Plains Indian mothers who are not abstainers report drinking substantially more alcohol (quantity) overall and more frequent drinking^{3,39} than South African and Italian mothers. While quantity of alcohol consumed per occasion and frequent consumption are necessary conditions that lead to fetal alcohol syndrome and partial FAS, these findings suggest that there are other factors (e.g., body mass, nutritional, environmental or genetic) that facilitate a more frequent occurrence of symptoms of FASD in South African Colored women who consume alcohol. Thus, in different populations, the same level of prenatal alcohol consumed, may not lead to similarly affected children.

This study supports the use of multiple abnormal syndromic findings together to make a diagnosis of severe FASD. Furthermore, it shows that although there are variations between ethnicities in morphological features, by using the syndromic features together and comparing affected children with normal controls within the same population, an accurate FASD diagnosis may be made. Alternatively, applying a single generalized set of nonspecific normative physical measures that were not sensitive to local, ethnic variations in morphology would not be properly sensitive for fetal alcohol syndrome and partial FAS diagnoses. This is important in a multi-ethnic population such as the U.S. In addition, demonstrated here is the concept that there are additional underlying factors that vary in different populations and affect the development of an FASD above and beyond that of the single effect of alcohol dosage. Some, of these additional factors await further study within multi-ethnic populations such as the United States and across populations.

Acknowledgments

We are indebted to the field staff in the United States, Italy, and South Africa who were instrumental in assisting in the collection of the child dysmorphology and maternal interviews data: Irene Lake, Rose Maestas, Mabel Granados, Sherlynn Herrera, Joan Alvord, Renee Parker, Mary White Country, Whitney Renville, Karen Goodhart, Jill Plumage, Margaret Anne Yellow Kidney; Daniela Fiorentino, Giovanna Corriale, Lucia Cupelli, Irene Di Stefano, Mar-cella Scamporrino, Anna Maria Galli, Fredrica Ceratti, Francesca De Rosa; Julie Croxford, Leslie Brooke, Anna Susan Marais, and Cudore Snell. We further acknowledge the efforts of Chandra Stellavato who assisted with data processing.

The research in the US and South Africa was supported in part by grants RO1AA09440 and RO1/UO1AA11685 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the NIH National Center on Minority Health and Health Disparities (NCMHD).

The Italian study was supported in part by NIAAA pilot project subcontract 53257 A-P1660-7802-211 CSM from San Diego State University as part of the International Consortium for the study of FASD (CIFASD) AA014800 and AA014828, and a grant from the health department of the government of the Lazio region, Assessorato alla Sanita della Regione Lazio, and a grant from SITAC OULUS.

REFERENCES

1. Stratton, KR.; Howe, CJ.; Battaglia, FC., editors. Fetal Alcohol Syndrome Diagnosis, Epidemiology, Prevention, and Treatment. Washington, DC.: National Academy Press; 1996.
2. Abel, EL. Fetal Alcohol Abuse Syndrome. New York, NY: Plenum Press; 1998.
3. May PA, Gossage JP. Estimating the prevalence of fetal alcohol syndrome: a summary. *Alcohol Res Health*. 2001; 25:159–167. [PubMed: 11810953]
4. May PA, Gossage JP, Kalberg WO, et al. Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis on in-school studies. *Devel Disabil Res Rev*. 2009; 15:176–192. [PubMed: 19731384]
5. Sampson PD, Streissguth AP, Bookstein FL, et al. Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder. *Teratology*. 1997; 56:317–326. [PubMed: 9451756]
6. Abel EL. An update on incidence of FAS: FAS is not an equal opportunity birth defect. *Neurotoxicol Teratol*. 1995; 17:437–443. [PubMed: 7565490]
7. May PA, Fiorentino D, Gossage JP, et al. Epidemiology of fetal alcohol spectrum disorders in a province in Italy: prevalence and characteristics of children in a random sample of schools. *Alcohol Clin Exp Res*. 2006; 30:1562–1575. [PubMed: 16930219]
8. Clarren SK, Randels SP, Sanderson M, Fineman RM. Screening for fetal alcohol syndrome in primary schools: a feasibility study. *Teratology*. 2001; 63:3–10. [PubMed: 11169548]
9. Streissguth AP, Randels SP, Smith DF. A test-retest study of intelligence in patients with fetal alcohol syndrome: implications for care. *J Am Acad Child Adolesc Psychiatry*. 1991; 30:584–587. [PubMed: 1823538]
10. Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. *Lancet*. 1973; 2:999–1001. [PubMed: 4127281]
11. Sullivan WC. A note on the influence of maternal inebriety on the offspring. *J Ment Sci*. 1899; 45:489–503.
12. Lemoine P, Harosusseau H, Borteyru JP, Menuet JC. Les enfants des parents alcooliques: anomalies observees a propos de 127 cas. *Ouest Med*. 1968; 21:476–482.
13. Armstrong EM, Abel EL. Fetal alcohol syndrome: the origins of a moral panic. *Alcohol Alcohol*. 2000; 35:276–282. [PubMed: 10869248]
14. Chudley AE, Conry J, Cook JL, Loock C, Rosales T, LeBlanc N. Public Health Agency of Canada's National Advisory Committee on Fetal Alcohol Spectrum Disorder. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. *CMAJ*. 2005; 172:S1–S21. [PubMed: 15738468]

15. Hoyme HE, May PA, Kalberg WO, et al. A practical clinical approach to the diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. *Pediatrics*. 2005; 115:39–47. [PubMed: 15629980]
16. Astley SJ, Clarren SK. Diagnosing the full spectrum of fetal alcohol-exposed individuals: introducing the 4-digit diagnostic code. *Alcohol Alcohol*. 2000; 35:400–410. [PubMed: 10906009]
17. Wattendorf DJ, Muenke M. Fetal alcohol spectrum disorders. *Am Fam Physician*. 2005; 72:279–285. [PubMed: 16050451]
18. Astley SJ. Comparison of the 4-digit diagnostic code and the Hoyme diagnostic guidelines for fetal alcohol spectrum disorders. *Pediatrics*. 2006; 118:1532–1545. [PubMed: 17015544]
19. May PA, Brooke LE, Gossage JP, et al. Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. *Am J Public Health*. 2000; 190:1905–1912. [PubMed: 1111264]
20. May PA, Gossage JP, Brooke LE, et al. Maternal risk factors for fetal alcohol syndrome in the Western cape province of South Africa: a population-based study. *Am J Public Health*. 2005; 95:1190–1199. [PubMed: 15933241]
21. May PA, Gossage JP, Marais AS, et al. The epidemiology of fetal alcohol syndrome and partial fetal alcohol syndrome in a South African community. *Drug Alcohol Depend*. 2007; 88:259–271. [PubMed: 17127017]
22. Jacobson JL, Jacobson SW. Prenatal alcohol exposure and neurobehavioral development: where is the threshold? *Alcohol Health Res World*. 1994; 18:30–36.
23. Adnams CM, Kodituwakku PW, Hay A, Molteno CD, Viljoen D, May PA. Patterns of cognitive motor development in children with fetal alcohol syndrome from a community in South Africa. *Alcohol Clin Exp Res*. 2001; 25:557–562. [PubMed: 11329496]
24. Day NL, Leech SL, Richardson GA, Cornelius MD, Robles N, Larkby C. Prenatal alcohol exposure predicts continued deficits in offspring size at 14 years of age. *Alcohol Clin Exp Res*. 2002; 26:1584–1591. [PubMed: 12394293]
25. Kodituwakku P, Coriale G, Fiorentino D, et al. Neurobehavioral characteristics of children with fetal alcohol spectrum disorders in communities from Italy: preliminary results. *Alcohol Clin Exp Res*. 2006; 30:1551–1561. [PubMed: 16930218]
26. Aragon AS, Coriale G, Fiorentino D, et al. Neuropsychological characteristics of Italian children with fetal alcohol spectrum disorders. *Alcohol Clin Exp Res*. 2008; 32:1909–1919. [PubMed: 18715277]
27. Aragon AS, Kalberg WO, Buckley D, Barela-Scott LM, Tabachnick BG, May PA. Neuropsychological study of FASD in a sample of American Indian children: processing simple versus complex information. *Alcohol Clin Exp Res*. 2008; 32:2136–2148. [PubMed: 18828799]
28. Mattson SN, Riley EP, Gramling LJ, Delis DC, Jones KL. Neuropsychological comparison of alcohol-exposed children with or without features of fetal alcohol syndrome. *Neuropsychology*. 1998; 12:146–153. [PubMed: 9460742]
29. Mattson SN, Calarco KE, Lang AR. Focuses and shifting attention in children with heavy prenatal alcohol exposure. *Neuropsychology*. 2006; 20:361–369. [PubMed: 16719629]
30. Mattson SN, Riley EP. A review of the neurobehavioral deficits in children with fetal alcohol syndrome or prenatal exposure to alcohol. *Alcohol Clin Exp Res*. 1998; 22:279–294. [PubMed: 9581631]
31. Streissguth AP, O'Malley K. Neuropsychiatric implications and long-term consequences of fetal alcohol spectrum disorders. *Semin Clin Neuropsychiatry*. 2000; 5:177–190. [PubMed: 11291013]
32. Robinson GC, Conry JL, Conry RF. Clinical profile and prevalence of fetal alcohol syndrome in an isolated community in British Columbia. *CMAJ*. 1987; 137:203–207. [PubMed: 3607663]
33. May, PA.; McCloskey, J.; Gossage, JP. Alcohol Use Among American Indians and Alaska Native: Multiple Perspectives on a Complex Problem. NIAA monograph 27. Bethesda, MD: U.S. Department of Health and Human Services; 2002. Fetal Alcohol Syndrome Among American Indians: Epidemiology, Issues, and Research Review.
34. Viljoen DL, Gossage JP, Adnams CM, et al. Fetal alcohol syndrome in a South African community: a second study of a very high prevalence area. *J Stud Alcohol*. 2005; 66:593–604. [PubMed: 16331845]

35. Quaid J, Kirkpatrick J, Nakamura R, Aase JM. Establishing the occurrence of FAS/FAE in a rural community. *Provider*. 1993; 18:71–75.
36. Duimstra C, Johnson D, Kutsch C, et al. A fetal alcohol syndrome surveillance pilot project in American Indian communities in the Northern Plains. *Pub Health Rep*. 1993; 108:225–229. [PubMed: 8464980]
37. May PA, Gossage JP, White-Country M, et al. Alcohol consumption and other maternal risk factors for fetal alcohol syndrome among three distinct samples of women before, during, and after pregnancy: the risk is relative. *Am J Med Genet C Semin Med Genet*. 2004; 127C:10–20. [PubMed: 15095467]
38. May PA, Gossage JP. New data on the epidemiology of adult drinking and substance abuse among American Indians of the northern States: male and female data on the prevalence, patterns, and consequences. *Am Indian Alsk Native Ment Health Res*. 2001; 10:1–25. [PubMed: 11698981]
39. Sobell LC, Sobell MB, Leo GI, Cancilla A. Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. *Br J Addict*. 1988; 83:393–402. [PubMed: 3395719]
40. Sobell, LC.; Sobell, MB. Alcohol consumption measures. In: Allen, JP.; Columbus, M., editors. *Assessing Alcohol Problems: A Guide for Clinicians and Researchers*. National Institute on Alcohol Abuse and Alcoholism Treatment Handbook Series 4. NIH Pub. No. 95–3745. Bethesda, MD: The Institute; 1995. p. 55-73.
41. Czarnecki DM, Russell M, Cooper ML, Salter D. Five-year reliability of self-reported alcohol consumption. *J Stud Alcohol*. 1990; 51:68–76. [PubMed: 2299853]
42. King AC. Enhancing the self-report of alcohol consumption in the community: two questionnaire format. *Am J Public Health*. 1994; 84:294–296. [PubMed: 8296958]
43. Dean, AG.; Dean, JA.; Burton, AH.; Dicker, RC. Stone. Mountain, GA: USD, Inc.; 1996. *Epi Info Version 6: A Word Processing, Database, and Statistics Program for Epidemiology on Microcomputers*.
44. SPSS Inc. *SPSS Base 11.0 for Windows User's Guide*. Chicago, IL: SPSS Inc.; 2006.
45. Viljoen DL, Croxford J, Gossage JP, Kodituwakku PW, May PA. Characteristics of mothers of children with fetal alcohol syndrome in the Western Cape Province of South Africa: a case control study. *J Stud Alcohol*. 2002; 63:6–17. [PubMed: 11925060]
46. May PA, Gossage JP, Marais AS, et al. Maternal risk factors for fetal alcohol syndrome and partial fetal alcohol syndrome in South Africa: a third study. *Alcohol Clin Exp Res*. 2008; 32:738–753. [PubMed: 18336634]

Table 1

Comparison of Measures Across Three Studies, Controls^a vs. FASD

Variable	Plains		Italy		South Africa		Significance p FASD Cases Compared
	Controls	FASD	Controls	FASD	Controls	FASD	
Mother's variables	n = 152	n = 52	n = 179	n = 39	n = 157	n = 66	
Reported drinking during index pregnancy, %	62.5	92.3	42.5	53.8	28.0	95.5	0.000 ^{b**}
Drinks consumed on typical drinking day, mean (SD)	4.3 (5.09)	7.6(6.27)	0.3 (0.52)	0.4 (0.60)	0.6 (1.82)	4.2(4.12)	0.000 ^{c**}
Binged (3+) during index pregnancy, %	51.4	83.7	0.8	5.4	13.3	74.1	0.000 ^{b**}
Child's variables	n = 221	n = 98	n = 256	n = 44	n = 172	n = 73	
Age (months), mean (SD)	85.4 (52.66)	92.8 (52.08)	80.2 (4.56)	79.7(4.14)	87.7 (6.49)	93.2(9.51)	0.000 ^{b**}
Height, centile, mean (SD)	57.7 (28.94)	27.9 (25.00)	53.3 (29.20)	37.5 (29.31)	25.9 (24.20)	5.6 (6.65)	0.000 ^{b**}
Weight, centile, mean (SD)	66.3 (28.59)	32.1(26.0)	58.7(30.14)	40.3 (30.52)	27.1 (25.75)	4.6 (5.79)	0.000 ^{b**}
Head circumference (OFC), centile, mean (SD)	60.3 (28.22)	24.5 (25.40)	47.4 (29.20)	25.6 (28.47)	28.3 (26.40)	4.2 (6.62)	0.000 ^{b**}
Smooth philtrum, %	10.3	82.7	18.2	90.9	63.4	86.3	0.000 ^{b**}
Long philtrum, %	34.5	41.8	40.9	54.5	36.0	45.2	0.328 ^b
Strabismus, %	1.3	6.1	3.1	6.8	1.7	4.1	0.380 ^b
Short interepillary distance, %	4.9	30.6	0.0	21.7	32.6	54.8	0.000 ^{b**}
Ptosis, %	1.3	9.2	3.1	6.8	4.7	15.1	0.149 ^b
Short intercanthal distance, %	3.1	13.3	11.3	20.5	19.2	23.3	0.000 ^{b**}
Flat nasal bridge, %	4.5	17.3	0.4	0.0	30.2	53.4	0.000 ^{b**}
Anteverted nostrils, %	4.5	19.4	10.9	22.7	13.4	26.0	0.006 ^{b**}
Palmer crease, %	21.5	32.7	22.9	36.4	27.3	42.5	0.380 ^b
Clinodactyly, %	6.3	7.1	32.6	54.5	44.2	53.4	0.000 ^{b**}
Camptodactyly, %	6.3	20.4	8.1	11.4	9.3	34.2	0.523 ^b
Heart murmur, %	1.8	5.1	0.8	2.3	4.1	13.7	0.055 ^b
"Railroad track" ears, %	11.7	19.4	6.6	13.6	3.5	15.1	0.007 ^{b*}

Variable	Plains		Italy		South Africa		Significance <i>p</i> Control Cases Compared	Significance <i>p</i> FASD Cases Compared
	Controls	FASD	Controls	FASD	Controls	FASD		
Dysmorphology score, mean (SD)	2.8 (2.60)	13.2 (4.53)	4.4 (3.43)	12.0 (4.05)	9.0 (4.62)	18.2 (4.62)	0.000 ^{b**}	0.000 ^{b**}

^aFASD is a category of anomalies under which there are four diagnoses: FAS, Partial FAS, alcohol-related neurodevelopmental deficits (ARND), and alcohol-related birth defects (ARBD). All the above cases are the two most dysmorphic forms of FASD, FAS and Partial FAS.

^b χ^2 of affirmative responses across three samples.

^c ANOVA of data across three samples.

* Significant at the Bonferroni .05 level.

** Significant at the Bonferroni adjusted alpha level of .0015.

Table 2
 Sequential Regression for (Square Root of) Dysmorphology Scores, Full Sample of FAS (PFAS Included) and Controls for Plains Indians, Italy Data, and South Africa Data

Variables	Plains Indians (N = 321)				Italy (N = 301)				South Africa (N = 246)			
	B	Standard Error of B	β	sr ² (Incremental)	β	Standard Error of B	β	sr ² (Incremental)	B	Standard Error of B	β	sr ² (Incremental)
Height (centile)	<-0.01	<0.01	-0.12	0.22*	<-0.01	<0.01	-0.07	0.11*	<-0.01	<0.01	-0.10	0.28*
Weight (centile)	<-0.01	<0.01	-0.10	0.08*	<-0.01	<0.01	-0.12	0.05*	-0.01*	<0.01	-0.18	0.12*
Head circumference (centile)	<-0.01	<0.01	-0.02	0.06*	-0.01	<0.01	-0.17	0.06*	-0.01*	<0.01	-0.20	0.06*
PFL (centile)	-0.01*	<0.01	-0.19	0.09*	-0.01	<0.01	-0.15	0.04*	-0.01*	<0.01	-0.15	0.06*
Narrow vermillion	0.70*	0.09	0.26	0.19*	0.60*	0.08	0.27	0.27*	0.48*	0.05	0.24	0.11*
Smooth philtrum	0.75*	0.08	0.27	0.07*	0.60*	0.09	0.25	0.09*	0.59*	0.06	0.28	0.12*
Long philtrum	0.77*	0.06	0.29	0.09*	0.61*	0.06	0.28	0.09*	0.34*	0.05	0.17	0.04*
Strabismus	-0.11	0.18	-0.01	<0.01	-0.12	0.18	-0.02	<0.01	0.06	0.15	0.01	<0.01
Interpupillary distance (centile)	-0.01	<0.01	-0.09	<0.01	N.A.	N.A.	N.A.	N.A.	<-0.01	<0.01	0.02	<0.01
Prosis	0.29	0.16	0.04	<0.01	0.52	0.17	0.09	0.01	0.39*	0.09	0.11	0.02*
Intercanthal distance (centile)	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	-0.01	<0.01	<-0.01	<0.01	-0.02	<0.01
Nasal bridge	0.43*	0.11	0.09	0.01*	0.30	0.53	0.02	<0.01	0.30*	0.6	0.15	0.03*
Anteverted nostrils	0.47*	0.11	0.10	0.01*	0.40*	0.09	0.12	0.02*	0.17	0.07	0.07	0.01
Aberrant palm crease	0.37*	0.07	0.13	0.02*	0.42*	0.07	0.17	0.03*	0.20*	0.05	0.10	0.01*
Fifth finger clinodactyly	0.20	0.12	0.04	<0.01	0.29*	0.06	0.13	0.02*	0.28*	0.05	0.15	0.02*
Campodactyly	0.34*	0.10	0.08	0.01*	0.33	0.11	0.09	0.01	0.19	0.07	0.07	0.01
Heart murmur	0.41	0.18	0.05	<0.01	0.26	0.30	0.02	<0.01	0.17	0.09	0.04	<0.01
Railroad ears	0.29*	0.09	0.08	0.01*	0.29	0.12	0.07	0.01	0.10	0.09	0.03	<0.01
Intercept	1.94	0.12			2.01	0.09			2.65	0.09		
			$R^2 = 0.86$				$R^2 = 0.78$				$R^2 = 0.88$	
			Adjusted				Adjusted				Adjusted	
			$R^2 = 0.85$				$R^2 = 0.77$				$R^2 = 0.87$	

Variables	Plains Indians (N = 321)			Italy (N = 301)			South Africa (N = 246)		
	<i>B</i>	β	sr ² (Incremental)	β	Standard Error of <i>B</i>	sr ² (Incremental)	β	Standard Error of <i>B</i>	sr ² (Incremental)
			<i>R</i> = 0.93			<i>R</i> = 0.89			<i>R</i> = 0.94

* *p* < .0015.

Table 3

Sequential Regression for (Square Root of) Dysmorphology Scores, Sample of FAS (PFAS Omitted) and Controls for Plains Indians, Italy Data, and South Africa Data

Variables	Plains Indians (n = 273)				Italy (n = 265)				South Africa (n = 228)			
	B	Standard Error of B	β	sr ² (Incremental)	B	Standard Error of B	β	sr ² (Incremental)	B	Standard Error of B	β	sr ² (Incremental)
Height (centile)	<0.01	<0.01	0.01	0.23*	<-0.01	<0.01	-0.08	0.10*	<-0.01	<0.01	-0.10	0.26*
Weight (centile)	-0.01*	<0.01	-0.15	0.09*	<-0.01	<0.01	-0.13	0.04*	-0.01*	<0.01	-0.18	0.13*
Head circumference (centile)	<0.01	<0.01	0.01	0.04*	-0.01*	<0.01	-0.16	0.05*	-0.01*	<0.01	-0.19	0.07*
PFL (centile)	-0.01*	<0.01	-0.15	0.07*	-0.01*	<0.01	-0.14	0.04*	-0.01*	<0.01	-0.15	0.05*
Narrow vermillion	0.64*	0.10	0.22	0.18*	0.58*	0.09	0.25	0.21*	0.48*	0.06	0.25	0.10*
Smooth philtrum	0.80*	0.10	0.27	0.07*	0.64*	0.10	0.25	0.09*	0.60*	0.06	0.29	0.13*
Long philtrum	0.89*	0.07	0.33	0.10*	0.65*	0.07	0.31	0.10*	0.35*	0.05	0.18	0.04*
Strabismus	0.02	0.21	<0.01	<0.01	-0.14	0.19	-0.02	<0.01	0.08	0.16	0.01	<0.01
Interpupillary distance (centile)	-0.01	<0.01	-0.09	0.01	N.A.	N.A.	N.A.	N.A.	<-0.01	<0.01	0.02	<0.01
Prosis	0.28	0.18	0.04	<0.01	0.69*	0.21	0.11	0.01	0.43*	0.10	0.12	0.02*
Intercanthal distance (centile)	<0.01	<0.01	0.03	<0.01	<-0.01	<0.01	-0.03	<0.01	<-0.01	<0.01	-0.04	<0.01
Nasal bridge	0.44*	0.12	0.10	0.01*	0.19	0.55	0.01	<0.01	0.30*	0.06	0.15	0.03*
Anteverted nostrils	0.65*	0.13	0.13	0.02*	0.48*	0.11	0.15	0.02*	0.21	0.08	0.08	0.01
Aberrant palm crease	0.40*	0.08	0.13	0.02*	0.45*	0.08	0.19	0.04*	0.20*	0.06	0.10	0.01*
Fifth finger clinodactyly	0.14	0.13	0.03	<0.01	0.30*	0.07	0.14	0.02*	0.30*	0.05	0.15	0.02*
Campodactyly	0.31	0.11	0.07	0.01	0.47*	0.13	0.13	0.01*	0.23*	0.07	0.09	0.01*
Heart murmur	0.39	0.18	0.05	<0.01	0.24	0.31	0.03	<0.01	0.16	0.11	0.04	0.01
Railroad ears	0.26	0.09	0.07	<0.01	0.32	0.13	0.08	0.01	0.11	0.10	0.03	<0.01
Intercept	1.89	0.13			1.98	0.10			2.62	0.09		
			Adjusted R ² = 0.86				Adjusted R ² = 0.75				Adjusted R ² = 0.87	
			R ² = 0.85				R ² = 0.73				R ² = 0.86	

Table 4

Fixed Effects (Averaged Over Children and Locations) For Two-Level Model of Square Root of Dysmorphology Score as Predicted From 17 Physical Variables (N = 868)

Effect	Parameter Estimate	Standard Error	t-Ratio <i>df</i> = 2	<i>p</i>
Height (centile)	-0.003	0.001	-2.30	.103
Weight (centile)	-0.005	0.001	-4.48	.090
Head circumference (centile)	-0.005	0.002	-3.06	.133
PFL (centile)	-0.010	0.001	-6.72	<.001
Narrow vermilion	0.595	0.682	8.73	<.001
Smooth philtrum	0.655	0.058	11.28	<.001
Long philtrum	0.561	0.101	5.54	.006
Strabismus	-0.070	0.110	-0.63	.592
Ptoxis	0.397	0.090	4.39	.104
Intercanthal distance (centile)	-0.001	0.001	-1.51	.226
Nasal bridge	0.387	0.063	6.09	.001
Anteverted nostrils	0.333	0.083	4.02	.163
Aberrant palm crease	0.336	0.064	5.25	.015
Fifth finger clinodactyly	0.264	0.040	6.54	<.001
Camptodactyly	0.286	0.064	4.47	.091
Heart murmur	0.297	0.107	2.76	.093
Railroad ears	0.224	0.075	3.00	.125
Intercept	2.197	0.19	11.44	<.001

Table 5

Random Effects-Results of Two-Level Model of Square Root of Dysmorphology Score as Predicted From 17 Physical Variables (N = 868)

Effect	Variance Component	Standard Deviation	χ^2 , <i>df</i> = 1	<i>p</i> (1-Sided)
Height (centile)	<0.001	0.001	2.30	.125
Weight (centile)	<0.001	0.001	1.20	.272
Head circumference (centile)	<0.001	0.003	10.32	.002
PFL (centile)	<0.001	0.002	2.75	.093
Narrow vermillion	0.009	0.096	5.43	.019
Smooth philtrum	0.005	0.070	2.59	.103
Long philtrum	0.027	0.165	21.96	<.001
Strabismus	0.009	0.096	0.86	>.500
Ptoxis	0.007	0.083	0.59	>.500
Intercanthal distance (centile)	<0.001	0.001	0.79	>.500
Nasal bridge	0.004	0.065	2.07	.146
Anteverted nostrils	0.013	0.114	3.99	.043
Aberrant palm crease	0.008	0.091	4.44	.033
Fifth finger clinodactyly	0.009	0.029	0.20	>.500
Campodactyly	0.004	0.066	1.63	.198
Heart murmur	0.011	0.105	1.86	.170
Railroad ears	0.008	0.090	1.92	.162
Intercept	0.102	0.319	23.69	<.001
Residual	0.212	0.460		