CANADIAN PALPEBRAL FISSURE LENGTH GROWTH CHARTS REFLECT A GOOD FIT FOR TWO SCHOOL AND FASD CLINIC-BASED U.S. POPULATIONS

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ABSTRACT

Background
Short palpebral fissure lengths (PFL) are one of three facial features that define the unique facial phenotype of fetal alcohol syndrome (FAS). Published PFL growth charts vary greatly in both rate and magnitude of growth, placing their accuracy and validity in question. New PFL growth charts were recently published to reflect a racial/ethnic cross section of Canadian girls and boys 6-16 years of age. PFLs were measured from digital facial photographs using the FAS Facial Photographic Analysis Software.

Objectives
Assess the goodness of fit of two U.S. populations (healthy children and children with prenatal alcohol exposure) when plotted on the Canadian, Hall, and other published PFL charts.

Methods
The PFLs of 106 healthy children and 822 children with prenatal alcohol exposure from Washington State were measured from digital facial photographs using the FAS Facial Photographic Analysis Software. Goodness of fit was assessed graphically and by computation of the mean PFL z-score.

Results
Our predominantly Caucasian, healthy group of children scattered along the mean growth curve on the Canadian charts (mean PFL z-score +0.2), and fell 1.6 SDs below the mean on the Hall chart (mean PFL z-score -1.6). The mean PFL z-score for the children with FAS was 2.4 SDs below the mean on the Canadian charts and 3.9 SDs below the mean on the Hall chart. African Americans were not a good fit.

Conclusion
The Canadian PFL charts were a good fit for our predominantly Caucasian populations of healthy U.S. school-aged children. Children with FAS continued to present with PFLs 2 or more SDs below the mean when plotted on the Canadian PFL charts, supporting the FAS PFL diagnostic criteria used by the FASD 4-Digit Diagnostic Code. Use of PFL charts normed for African Americans is recommended. Updated PFL charts for 0-6 years of age are vital to prevent an artificial over-estimation of short PFLs in this age group.

Key Words: *Fetal alcohol syndrome (FAS); fetal alcohol spectrum disorders (FASD); FASD 4-Digit Diagnostic Code; palpebral fissure length*

Short palpebral fissure length (PFL) is a minor physical anomaly noted in several syndromes including fetal alcohol syndrome (FAS) The PFL is the distance between the endocanthion and exocanthion landmarks (Figure 1). Published charts depicting normal growth of the PFL have been generated from a variety of populations (both healthy and clinical) using a variety of measurement techniques (tape measures, rulers, calipers, photos).[1-9] The size and rate of growth of the PFL vary tremendously across these charts (Figure 2). This has led some to question their accuracy/validity.[10-13] As long ago as 1966, an opthalmalogist named Fox[13] expressed the following concern "literature on the subject (palpebral fissure) is scarce; where it exists no two authorities seem to agree on the size, shape and proportions of the lid fissure".

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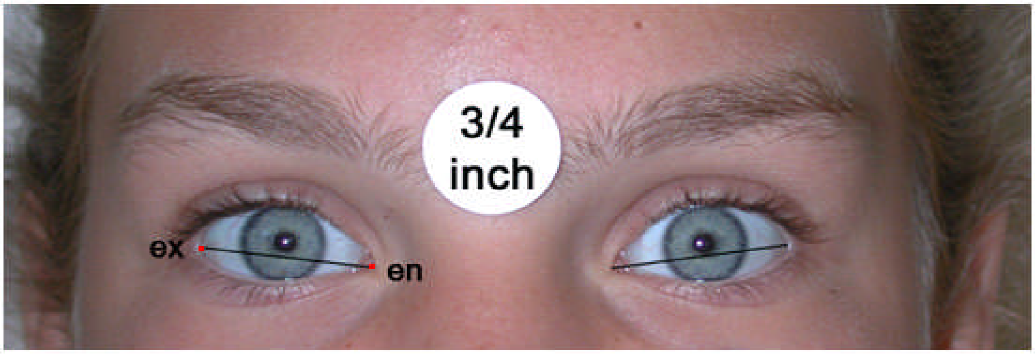

FIG. 1 The palpebral fissure length (PFL) is the distance from the inner corner of the eye (endocanthion landmark) to the outer corner of the eye (exocanthion landmark). The right and left PFLs were measured in this study using the FAS Facial Photographic Analysis Software.[21] A ¾ inch sticker (19.05 mm) is placed between the patient's eyebrows to serve as an internal measure of scale.

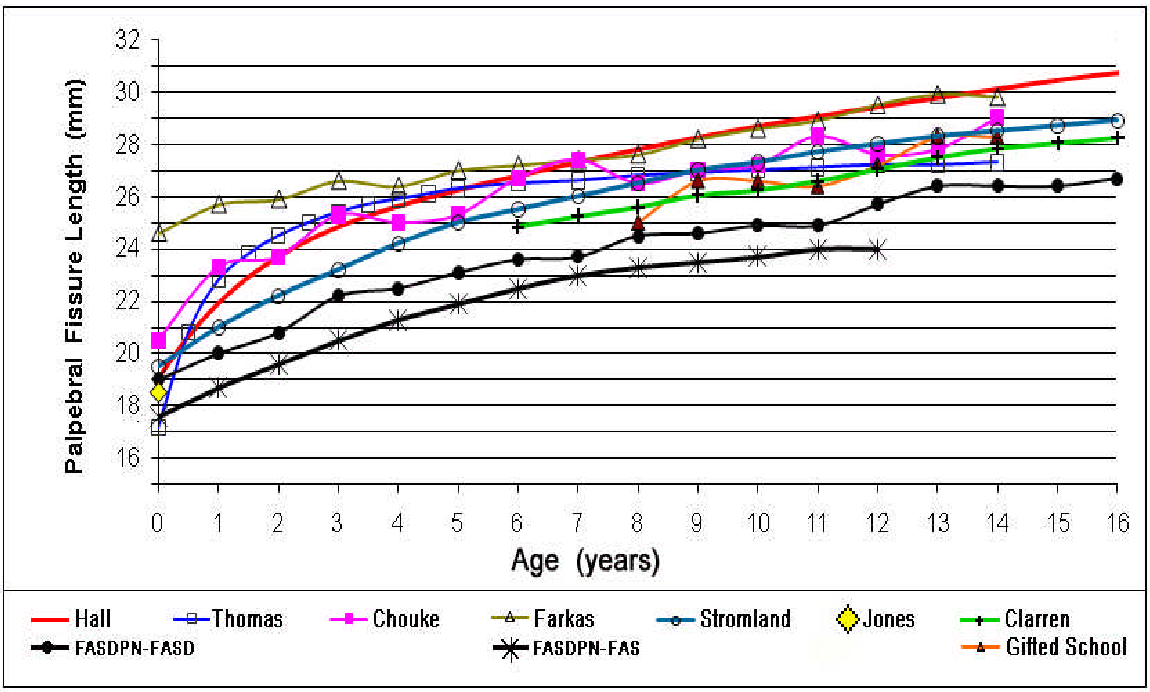

FIG. 2 Comparison of the mean PFL growth curve from published charts depicting normal growth (Hall et al.[5], Thomas et al.[9], Chouke[2], Farkas[3], Stromland et al.[8], Jones et al.[7], and Clarren et al[12]) and selected study samples from Washington State: (children attending a gifted school program (study population 1); and two populations of children diagnosed at the WA State FAS DPN: those with prenatal alcohol exposure (study population 4), and the subset with FAS (study population 3).

When the Washington State FAS Diagnostic & Prevention Network (FAS DPN) first opened in 1993, the Caucasian PFL growth chart constructed by Hall et al[5] was selected for use. The Hall chart is a composite of four previously published charts: Chouke[2]; Farkas[14], Laestadius[15], and Thomas.[9] Chouke[2] used a sliding caliper to measure the PFLs of 258 North American Caucasian patients and medical students, aged 1 week to 35 years of age, from St. Louis Children's Hospital. It is important to note that the purpose of his study was to ascertain the cause of the epicanthal fold, thus all patients showed some degree of the "Mongolian Fold". Farkas[14] used a sliding caliper to measure

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the PFLs of 2,326 healthy Caucasian males and females, aged newborn to 25 years of age, residing in Alberta, Ontario, and Quebec, Canada. Thomas[9] derived a mathematical model of PFL growth from 348 North American Caucasian children 29 weeks to 14 years old. The PFLs were obtained from Chouke[2] and Jones et al.[7] Jones et al[7] used a ruler to measure the PFLs of 200 North American Caucasian newborns (32 to 40 weeks gestation). Laestadius[15] measured the innercanthal distance (distance between the right and left endocanthions) and the outer orbital distance (distance between the outermost edges of the bony orbits) of 472 Caucasian individuals, premature to adult, from clinical and school populations. Laestadius did not measure PFL. If one subtracted the innercanthal distance from the outer orbital distance and divided the outcome by two, one could compute the mean distance from the endocanthion to the outer orbital ridge. The distance from the endocanthion to the outer orbital ridge, by definition, is not the PFL. This measure would exceed the PFL by 4 to 5 mm, as depicted in Figure 1 published by Clarren et al[12] Ten years after the publication of the Hall PFL charts, Stromland et al[8] published PFL charts for white, Scandinavian, healthy males (n=291) and females (n-322), 1 month to 18 years of age, using photogammetry. And most recently, in 2010, Clarren et al[12] published PFL charts for a racial/ethnic cross section of Canadian girls (n=1,194) and boys (n=903), 6-16 years of age. PFLs were measured from digital facial photographs using the FAS Facial Photographic Analysis Software.

Over the years, it became apparent that the PFLs of Caucasian patients evaluated in the WA FAS DPN were frequently 2 or more standard deviations (SD) below the mean depicted on the Hall PFL chart. One plausible explanation for this observation could be that the PFL is especially vulnerable to the adverse impact of prenatal alcohol exposure. To test this theory, Dr. Astley measured a small, convenient sample of volunteers (the FAS DPN clinical staff, including herself) to see where they fell on the Hall PFL charts. Surprisingly, most fell two or more SDs below the mean. The individual with the largest PFLs fell 1 SD below the mean. This outcome suggested the Hall PFL chart over-estimated the normal size of a PFL. To further assess the accuracy of the Hall chart, the PFLs of 90 healthy children attending a Washington State elementary school for gifted children were measured with Human Subjects Review Board approval and parental consent in 1999. A gifted school program was selected to minimize risk of adverse outcomes from prenatal alcohol exposure. The average PFL of the 90 predominantly Caucasian children from 6.0 to 16.0 years of age was 1.6 SDs below the mean when plotted on the Hall PFL chart (Figure 3, Table 1). Once again, the Hall PFL charts appeared to over-estimate the normal size of a PFL. This outcome was not unique to the Hall PFL chart. Based on Figure 2, all published PFL charts[2,3,5,.8,.9] appeared to over-estimate the size of the PFL observed in our samples by 1-3 mm (or 4-12%). The magnitude of this over-estimate is clinically concerning, since 1.5 mm is roughly equivalent to 1 SD. Until new, more accurate PFL charts became available, the FAS DPN chose to continue using the Hall PFL chart because even though it appeared to over-estimate the length of a normal palpebral fissure, the rate of growth (slope) depicted in the chart best matched the rate of growth observed across the lifespan in both our clinic and normal populations (Figure 2). Use of a PFL growth chart that matched our rate of growth assured that the PFL would be over-estimated equally across the lifespan, preventing age-dependent diagnostic misclassification. Although the best error is no error at all, the next best option is to select a chart that produces a consistent error, rather than an inconsistent error. If one uses a PFL chart that over-estimates the length of a normal palpebral fissure, the chart will over-estimate the prevalence of short palpebral fissures. This, in turn could lead to a risk of over-diagnosis of FAS. We were aware of this risk, but observed that when a patient presented with all of the features of FAS as defined by the 4-Digit Code (growth deficiency, all three FAS facial features, CNS abnormalities, and alcohol exposure), their PFLs were not just 2 SDs below the mean (as required by the diagnostic guidelines), but were always 3-4 SDs below the mean. It appeared the Hall PFL charts were not leading to an over-diagnosis of FAS in our clinics. It was always our belief that the Hall PFL charts over-estimated the PFL by 1-2 mm. With the creation of the Canadian PFL charts[12], we now have an opportunity to test this hypothesis.

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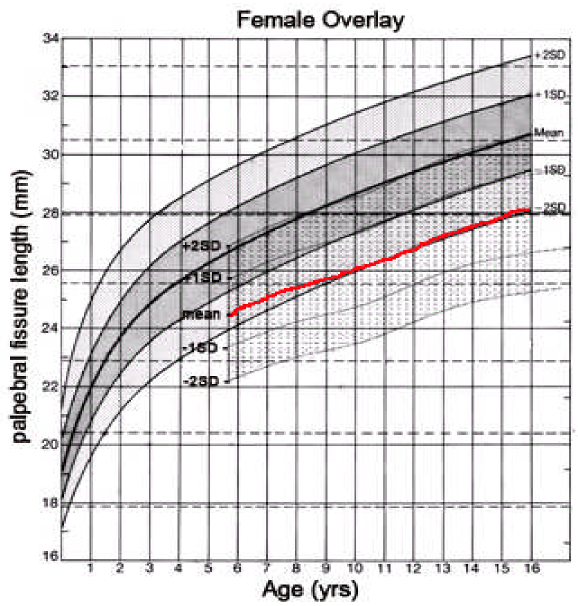

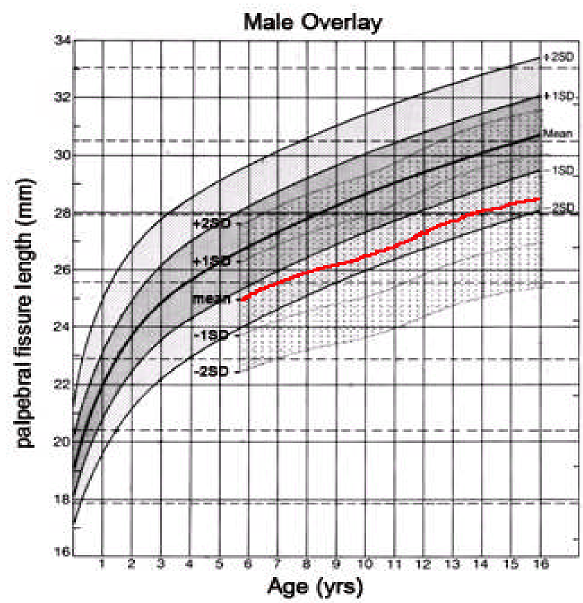

3A **3B**

FIG. 3 Illustration of the contrast between the Canadian[12] and Hall[5] PFL growth charts. The Canadian female (A) and male (B) PFL growth charts (speckled backgrounds), for children 6 to 16 years of age, are overlaid on the Hall PFL growth chart for both genders, 0-16 years of age. The red lines on the overlays reflect the mean PFL growth curve. The mean PFL growth curve (red line Fig. 3A) for Canadian females aligns with the -2.0 SD growth curve on the Hall PFL chart. The mean PFL growth curve (red line Fig. 3B) for Canadian males aligns with the -1.5 SD growth curve on the Hall PFL chart.

TABLE 1 Mean PFL z-scores* for the four study populations when plotted on the Hall[5] and Canadian[12] PFL charts.

Study Population	N	Hall[5] PFL z-score mean (SD)	Canadian[12] PFL z-score mean (SD)	Age range years
1. Healthy School-based				
Both genders	90	-1.59 (0.90)	+0.17 (0.82)	6.0 - 16.0
Girls	42	-1.80 (0.83)	+0.17 (0.87)	6.0 – 16.0
Boys	48	-1.40 (0.93)	+0.18 (0.82)	6.0 – 16.0
2. Healthy MRI Controls				
Both genders	16	-1.66 (0.69)	+0.19 (0.67)	8.3 – 15.8
Girls	8	-1.76 (0.49)	+0.16 (0.84)	8.3 – 14.4
Boys	8	-1.55 (0.87)	+0.22 (0.51)	8.4 – 15.8
3. FAS DPN: FAS				
Both genders	22	-3.86 (0.82)	-2.36 (0.97)	6.2 – 13.8
Girls	11	-4.18 (1.02)	-2.51 (1.22)	6.6 – 13.8
Boys	11	-3.55 (0.40)	-2.21 (0.65)	6.2 – 12.6
4. FAS DPN: prenatal alcohol exposed				
Both genders	822	-2.61 (1.45)	-1.05 (1.46)	6.0 – 16.9
Girls	320	-2.74 (1.52)	-1.04 (1.61)	6.0 – 16.9
Boys	502	-2.54 (1.41)	-1.06 (1.36)	6.0 – 16.9

* A z-score reflects how many standard deviations a data point is from the normal population mean. The mean PFL for a healthy population would be expected to have a mean z-score close to 0.0. The mean PFL for a population with FAS should have a mean z-score at or below -2.0.

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METHODS

Primary Objectives

The primary objectives of this study were to:

1. Compare the Canadian[12] and Hall[5] PFL normal growth charts.
   a. Graphically overlay digital images of the two charts to compare the positions of the mean, ±1SD, and ±2SD growth curves.
2. Determine the goodness of fit of a healthy U.S. population on the Canadian[12] and Hall[5] PFL normal growth charts:
   a. Plot the PFLs of 106 healthy U.S. children on the Canadian and Hall PFL normal growth charts to visually assess goodness of fit. A good fit would be depicted by U.S. PFLs scattering along the mean PFL growth curves on the two charts.
   b. Compute PFL z-scores for the 106 healthy U.S. children (using on the population mean and 1-SD levels depicted in the Canadian and Hall PFL normal growth charts) to quantitatively assess goodness of fit. A good fit would be depicted by a mean PFL z-score near zero.
3. Determine how far below the mean a U.S. population of patients with FASD fall on the Canadian[12] and Hall5 normal PFL charts.
   a. Compute the mean PFL z-scores for 1) 822 patients with prenatal alcohol exposure and 2) the subset of 22 with full FAS, using the population mean and 1-SD levels depicted in the Canadian and Hall PFL normal growth. One would expect the mean PFL z-scores for the alcohol exposed group to fall between zero and -2.0. The mean PFL z-score for FAS should be at or below -2.0.
   b. Plot the mean PFL growth curve for the 822 patients with prenatal alcohol exposure and the subset of 22 with full FAS on a composite graph of published mean PFL growth curves to visually compare and contrast.
4. Compare the mean PFL growth curves across several published PFL normal charts.
   a. Plot the mean PFL growth curves for the following published PFL charts[2,3,5,7,8,9,12] and the healthy and FASD populations from our U.S. healthy and alcohol-exposed study samples.
5. Assess the impact of race (specifically: Caucasian versus African American) on PFL.
   a. Compare the mean PFL between Caucasian and African American among the WA FAS DPN populations.

Study Populations

PFLs from four existing U.S. (Washington State) study populations were used in this study. The populations were restricted to those individuals from 6.0 to 16.9 years of age to match the age range portrayed in the Canadian PFL charts. All datasets were collected with Human Subject Review Board approval.

1. <u>Healthy School Population (1999)</u>: 90 healthy children (6.0-16.0 years of age) from a Washington State elementary school for gifted children. (47% female, 89% Caucasian, 1% African American). A gifted program was selected to minimize the risk of prenatal alcohol exposure.
2. <u>Healthy MRI Control Study Population (2003)</u>: 16 healthy children (8.3-15.8 years of age) enrolled as controls in a University of Washington FASD magnetic resonance study.[16-19] (50% female, 81% Caucasian, 6% African American). Prenatal alcohol exposure was confirmed absent.
3. <u>FAS Clinical Population (1993-2005)</u>: 22 individuals (6.2-13.8 years of age) with a 4-Digit Diagnosis of FAS (Diagnostic categories A and B) from the WA State FAS DPN clinical database[20] (50% female, 73% Caucasian, 5% African American).
4. <u>Alcohol-Exposed Clinical Population (1993-2005)</u>: All 822 individuals (6.0-16.9 yrs of age) receiving a FASD diagnostic evaluation at the WA State FAS DPN[20] (39% female, 49% Caucasian, 7% African American, 10% FAS/Partial FAS, 33% Static Encephalopathy/Alcohol Exposed, 52% Neurodevelopmental Disorder/Alcohol Exposed). All had confirmed prenatal alcohol exposures.

Acquisition and measurement of digital facial photographs.

All PFLs were measured by one individual (SJA) from digital facial photographs taken by one photographer (SJA) using the FAS Facial Photographic Analysis Software.[21] Briefly, over

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the past two decades, standardized digital frontal facial photographs were obtained for the subjects in the four clinical, research, and school-based populations described above. For study population 1 (the school population) only the eyes were photographed to maintain confidentiality. Photographic standardization included no left-to-right rotation of the head, camera lens aligned in the subject's Frankfort horizontal plane (see video animation posted on FAS DPN website), and eyes fully open so the endocanthion and exocanthion landmarks were clearly visible (Figure 1). A ¾ inch (19.05 mm) paper sticker was placed on the forehead between the eyebrows as an internal measure of scale. To measure the PFLs, the digital photos are opened into the FAS Facial Photographic Analysis Software. The User enters the subject's gender, birth date, photo date, and the size of the internal measure of scale (3/4 inch sticker on forehead). The User measures the width of the paper sticker and the lengths of the right and left palpebral fissures in the photos using mouse-controlled distance measuring tools provided in the software. A video demonstration of the FAS Facial Photographic Analysis Software is posted on the FAS DPN website. The software computes the subject's age in years, computes the right and left PFLs in mm, and computes the PFL z-score based on which normal PFL growth charts the User selected (Caucasian[5], or African American[6]).

Plotting PFLs of healthy U.S. populations on the Canadian and Hall PFL growth charts.
The PFLs of the two healthy U.S. study populations (study populations 1 and 2) were plotted on the male and female Canadian[12] PFL charts and the Hall[5] PFL chart to visually assess how well the U.S. populations clustered around the mean growth curves (Figures 4 a, b, and c).

Computation of PFL z-scores:
PFL z-scores were computed for each subject based on the means and SDs depicted in the Canadian[12] and Hall[5] PFL charts. A z-score reflects the number of standard deviations (SD) a PFL is above or below the population mean depicted on the normal growth chart for that individual's age. Z-scores provide a quantitative measure of where the four study populations fell on the Canadian and Hall PFL charts. The formula for the PFL z-score is as follows: PFL z-score = ((population mean PFL in mm) – (subject's PFL in mm)) / ((population mean PFL in mm) – (population 1 SD PFL in mm)). For example, if a 10 year old girl had a PFL = 24.0 mm, her PFL z-score calculated based on the Canadian PFL chart for girls would be ((26.03 – 24.0)/(26.03-24.76)) = -1.6. In other words, the girl's PFL is 1.6 SDs below the mean for a 10 year old girl as depicted on the Canadian PFL chart.

PFL z-scores were computed for each subject based on the population means and SDs depicted in both the Canadian[12] and Hall[5] normal PFL growth charts. To generate the z-scores, the mean and 1 SD lines for the Canadian and Hall PFL charts were digitally traced to generate x,y coordinates along the full length of the growth curves. These x,y coordinates were then used to generate 6th order polynomial best-fit formulas of each line. The formula's predicted the lines with R-squares greater than 0.9999999 (reflecting a perfect fit). These formulas were also used to create a PFL z-score calculator for the Canadian and Hall PFL growth charts posted on the FAS DPN website.

Overlay of Canadian and Hall PFL charts.
Adobe Photoshop CS2[22] was used to overlay captured digital images of the Canadian and Hall PFL charts (Figure 3). This provided a visual comparison of the contrasts in the mean, $\pm$1 SD, and $\pm$2 SD growth curves for individuals 6-16 years of age.

Statistical Analyses
SPSS 14.0[23] was used for all statistical analyses. Chi-square tests and t-tests were used to compare proportions and mean between two groups, respectively. Two-tailed p-values < 0.05 were interpreted as statistically significant.

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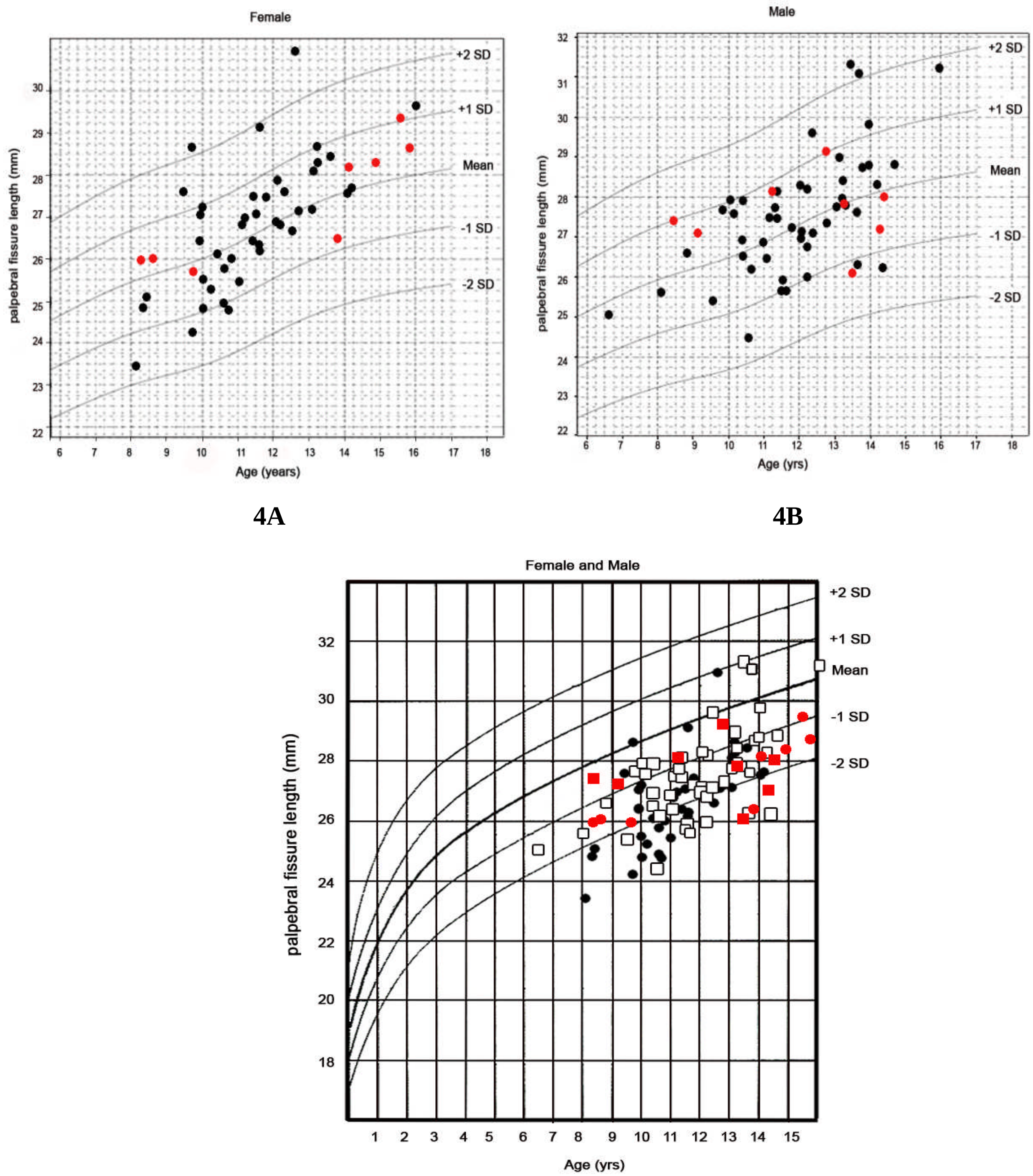

4A **4B**

4C

FIG. 4 Scatter plots illustrating the goodness of fit of our two healthy U.S. study populations (study populations 1 and 2) on the Canadian[12] and Hall[5] PFL charts. **A**) Canadian female PFL growth chart with the females from the healthy school population (black circles) and healthy MRI control group (red circles) plotted. **B**) Canadian male PFL growth chart with the males from the healthy school population (black circles) and healthy MRI control group (red circles) plotted. **C**) Hall PFL chart for males and females combined with the healthy school population (females: black circles, males black outlined squares) and the healthy MRI control group (females: red circles, males red squares) plotted. Plots A and B reflect a good fit (mean PFL z-scores range from +0.17 to +0.19). Plot C reflects a poor fit (mean PFL z-score = -1.6). These healthy groups of children are depicted on the Hall PFL chart as having PFLs on average 1.6 SDs below the mean (reflecting a poor fit). These same children are depicted as having PFLs on average 0.2 SDs above the mean when plotted on the Canadian PFL charts (reflecting a good fit).

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RESULTS

Objective 1. Graphic comparison of Canadian and Hall PFL normal growth charts.
When the Canadian PFL charts are overlaid on the Hall PFL chart, the mean PFL growth curves for Canadian males and females fall 1.5 and 2.0 SDs below the mean, respectively on the Hall PFL growth chart (Figure 3).

Objective 2. Goodness of fit of the healthy U.S. groups on the Canadian and Hall PFL normal growth charts.
The mean PFL of the 106 predominantly Caucasian, healthy U.S. children (90 school-based children and 16 healthy children enrolled as unexposed controls in a MRI study) scatter along the mean PFL growth curve on the Canadian PFL charts (Figures 4A and B). The mean PFL z-scores for the school and MRI study groups were +0.17 and +0.19 respectively (Table 1). Both the scatter plots and mean z-scores are reflective of a very good fit with the Canadian PFL charts. In contrast, these same children scatter, on average, 1.6 SDs below the mean PFL growth curve on the Hall PFL chart (Figure 4C, Table 1) demonstrating a poor fit. The Canadian PFL charts identify these children as having normal PFLs. The Hall PFL charts identify these children as having PFLs that are, on average, 1.6 standard deviations below normal.

Objective 3. Goodness of fit of the U.S. group with FASD on the Canadian and Hall PFL normal growth charts.
The mean PFL z-score for the 22 children diagnosed with full FAS from the WA FAS DPN clinics was 2.4 SDs below the mean on the Canadian PFL charts and 3.9 SDs below the mean on the Hall PFL charts (Table 1, Figure 2). These outcomes document the PFL for a child with FAS continues to fall 2 or more SDs below the mean when the Canadian PFL charts are used. The mean PFL z-score for the larger population of children with prenatal alcohol exposure was 1.1 SDs below the mean on the Canadian PFL charts and 2.6 SDs below the mean on the Hall PFL charts (Table 1, Figure 2). As hypothesized above, when the clinical population is expanded to include all children with prenatal alcohol exposure (not just the subset with FAS), the mean PFL z-score would still fall below the population mean, but not as far below the mean as the subgroup with full FAS. Twenty-five percent of the children with prenatal alcohol exposure had PFLs two or more SDs below the mean on the Canadian PFL charts. Sixty-eight percent of these children had PFLs two or more SDs below the mean on the Hall PFL chart.

Objective 4. Graphic comparison of the mean PFL growth curves across published PFL normal growth charts.
The mean PFL growth curves vary considerably in magnitude and slope across the published PFL normal growth charts[2,3,5,9,8,12] (Figure 2). All present with mean PFLs 0.5 to 2.0 mm greater than that depicted in the Canadian PFL charts. The mean PFL growth curves for the WA State FAS DPN patient population (all FASD and the subset with FAS) have the same rate of growth depicted in the Canadian PFL growth curve, but fall 1 and 2 SDs below the mean Canadian PFL growth curve respectively, as expected.

The greatest variability across the mean PFL growth curves occurs among children under 6 years of age. The rate of growth in the Thomas[9], Hall[5], and Chouke[2] charts, from birth to 4 years of age, is substantially faster than that depicted in the Farkas[3] and Stromland[8] charts. It is important to note that the Hall[5] chart is a composite of Thomas[9], Chouke[2], Farkas[15], and Jones.[7] This rate of growth is not observed in the FAS DPN clinical sample.

Objective 5. Assess the impact of race (specifically Caucasian versus African American) on PFL.
Of the 822 patients with prenatal alcohol exposure from the FAS DPN clinic between 6.0-16.9 years of age, 400 were Caucasian and 54 were African American. These two groups did not differ significantly in mean age, gender, or FASD diagnostic classification. The mean PFL for the African Americans (26.5 mm, 2.0 SD) was 1.5 mm longer than the mean PFL of the Caucasians (25.0 mm, 2.1 SD) ($t = 5.0$, $p < 0.001$) (Figure 5). A 1.5 mm difference is equivalent to 1 SD on the Canadian PFL chart. In other words, if these two racial groups were plotted on the Canadian male and female PFL charts, the mean PFL z-score for the African American group (-0.1, 1.3 SD) would be 1 SD larger than the mean PFL z-score for the Caucasian group (-1.2, 1.4 SD) ($t = 6.0$, $p < 0.001$). Not only is the African American group 1 SD higher on the Canadian PFL chart, but they fall along the mean PFL growth curve

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(reflecting normal growth). One would expect an alcohol-exposed group to fall below the mean (like the Caucasian alcohol-exposed group does). There were not a sufficient number of African Americans in our two healthy study populations (populations 1 and 2) to accurately compare PFLs between healthy, unexposed African Americans and Caucasians. There were, however, 105 Caucasian children and 7 African American children evaluated in the FAS DPN clinics whose suspected prenatal alcohol exposures could not be confirmed. The mean PFL for these 7 African Americans (26.2 mm, 1.9 SD) was also 1.6 mm longer than the mean PFL of the 105 Caucasians (24.6 mm, 2.2 SD) ($t = 1.9$, $p = 0.05$).

DISCUSSION

The Canadian PFLs charts[12] provide a much needed update in normal PFL growth from 6.0 to 16.9 years of age across a large, healthy, school-based, racially diverse sample. The current study demonstrates the Canadian PFL norms are a good fit for the PFLs we observed in two predominantly Caucasian, healthy, U.S. (Washington State) school and population-based samples of children. As a result, we have posted a free PFL z-score calculator on our FAS DPN website that will allow clinics to compute a patient's PFL z-score (based on the means and SDs depicted in the Canadian PFL charts) by entering the patient's age, gender, and PFL. We will also include the Canadian PFL charts as one of several PFL growth charts Users may select to use in the next version of the FAS Facial Photographic Analysis Software. The Canadian PFL norms also performed as we would have anticipated for our large, racially diverse, alcohol-exposed population evaluated in the WA State FASD diagnostic clinics. Children with FAS continued to present with PFLs 2 or more SDs below the mean when plotted on the Canadian PFL charts, supporting the FAS PFL diagnostic criteria (PFL 2 or more SDs below the mean) used by the FASD 4-Digit Diagnostic Code.[10] When the clinical population was expanded to include all children with prenatal alcohol exposure (not just the subset with FAS), the mean PFL z-score (-1.0) still fell below the population mean, but not as far below the mean as the subgroup with full FAS. The only subgroup that did not appear to be a good fit was our African American group.

It is well established in the published literature that African American's have significantly longer PFLs than Caucasians.[1,3,4] African Americans in our FASD clinical population had PFLs that were on average 1.5 mm longer (or 1 SD higher on the Canadian PFL growth charts) than Caucasians, across the lifespan (Figure 5). This magnitude of difference was both clinically and statistically significant, and consistent with the magnitude of difference reported for healthy populations of African Americans and Caucasians.[1,3,4] Starting at birth, Fuchs et al[4] reported the PFL was 1.5 mm longer among African American term neonates (20.0 mm, 2.0 SD) compared to Caucasian neonates (18.5mm, 1.3 SD) (7). Among adults, Barretto et al[1] reported the mean PFLs for African American women and men were 31.5 mm and 32.3 mm, respectively. These measures are on average 2.4 mm longer than PFLs for Caucasian women (29.4 mm) and men (29.5 mm). Farkas[3] reported the mean PFLs for African American adult women and men were 32.3 mm and 32.9 mm, respectively. These measures were on average 1.7 mm longer than the mean PFLs for Caucasian women (30.7 mm) and men (31.3 mm). Although the Canadian PFL charts are based on a racially diverse sample, the proportion of African Americans (2.5%) would not be sufficient to overcome this magnitude of difference in PFL between Caucasians and African Americans. It is well understood that norms based on multiracial groups will marginally over or under estimate the growth of individuals who are indigenously at the upper and lower boundaries of the physical spectrum. Clarren et al[12] created separate male and female PFL charts because of their 0.5 mm difference in PFL. The magnitude of difference between African American and Caucasian PFLs is 1.5 to 2.4 mm. This magnitude of difference warrants the use of PFL charts normed to African Americans. African American PFL normal growth charts exist[1,3,4,6], but they too would undoubtedly benefit from an update. The FAS DPN uses the Iosub et al[6] African American PFL charts for African American patients because they provide norms for children. A 10 year old African American boy with a PFL of 26.5 mm would fall directly on the mean using the Canadian multiracial chart for boys (PFL z-score 0.0), 1.6 SDs below the mean on the Hall Caucasian PFL chart, and 2.1 SDs below the mean on the Iosub[6] African American PFL charts.

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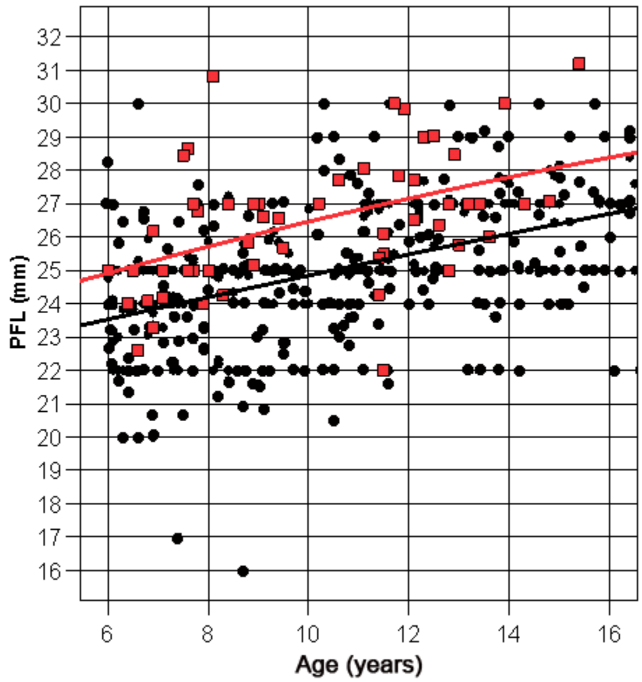

FIG. 5. Among the patients with prenatal alcohol exposure (study population 4), African Americans (red squares, red best linear-fit line) had significantly larger PFLs (mean = 26.5 mm, 2.0 mm SD) than the Caucasians (black circles, black best linear-fit line) (mean = 25.0mm, 2.1 mm SD). Age, gender, and FASD diagnostic classification were comparable between the two groups.

The Canadian PFL charts are a valuable clinical resource for use with patients 6 years of age and older. The absence of updated PFL charts for children under six years of age, however, poses quite a dilemma, especially in FASD diagnostic clinics where accurate interpretation of the PFL is critical to the accurate diagnosis of FAS. If a clinic uses the Canadian PFL charts for children 6 years of age and older, they will have to use one of the other currently published PFL charts for children under 6 years of age.

This will result in an abrupt increase in PFL as one transitions from the Canadian charts for older children to other published PFL charts for younger children (Figure 5). This, in turn, will create what appears to be a higher prevalence of short PFLs among children under age 6 versus over age 6. To illustrate this-the mean PFL for a 6-year-old boy is 25 mm on the Canadian[12] chart. The mean PFL for a 5.9-year-old boy leaps to 26.5 mm to 27.2 mm on the Thomas et al[9], Hall et al[5], and Farkas[3] charts. To further illustrate-a PFL of 25 mm reflects the mean PFL for a 6-year-old boy on the Canadian[12] charts. This same PFL reflects the mean PFL for a 5-year-old on the Stromland et al[8] chart, a 4-year-old on the Chouke[2] chart, a 3-year-old on the Hall et al[5] chart, a 2.3-year-old on the Thomas et al[9] chart, and a 6-month-old on the Farkas[3] chart. Updated PFL growth charts for children birth to 6 years of age are needed immediately. The U.S. National Children's Study[24] could serve as an excellent source of data to generate these norms. The National Children's Study is a prospective longitudinal observational study that will examine the effects of the environment and genetics on the growth, development, and health of thousands of children across a representative U.S. sample, following them from before birth until age 21 years.

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