NORMAL DISTRIBUTION OF PALPEBRAL FISSURE LENGTHS IN CANADIAN SCHOOL AGE CHILDREN

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ABSTRACT

Background
Fetal alcohol syndrome (FAS) includes the facial dysmorphic feature of short palpebral fissures (PFs) and short PFs are a key physical marker for identifying children with FAS and some other rarer conditions. There is concern that normative data on PFs now available may not reflect all racial/ethnic groups and might be inaccurate in general.

Objectives
To accomplish a large population based study that would accurately determine normative PF values across the full diversity of the Canadian school age population.

Methods
A normative sample of school age children was identified in Vancouver, British Columbia and Winnipeg, Manitoba to reflect the diversity of racial and national groups in Canada. The sample included students in grades 2, 4, 6, 8, and 10 from 17 schools in Vancouver and 31 schools in Winnipeg. Schools were selected based on racial diversity obtained from data from the 2001 Statistics Canada census. 1064 students in Vancouver and 1033 students in Winnipeg were photographed in a standardized way. Photographs were analyzed using a computerized method.

Results
Analysis demonstrated that PFs do grow with age and there is a slight but meaningful difference between boys and girls in each age group. It is possible to define Canadian standards without reference to racial or ethnic origin.

Conclusion
Mean results with norms and standard deviations are presented in figures for clinical use and are clinically smaller than those found in the most commonly used reference book.

Key Words: *fetal alcohol syndrome (FAS), fetal alcohol spectrum disorders (FASD), diagnostic criteria, palpebral fissures, normal values*

Variations in facial features have long been used by physicians and other clinicians to aid in the recognition of specific dysmorphic conditions.

A diagnosis of fetal alcohol syndrome (FAS) is made when a patient, exposed to ethanol in gestation, is found to have abnormality in three areas: diminished growth, facial features and central nervous system.[1] Not everyone exposed to alcohol *in utero* is adversely impacted by this exposure and those that are adversely impacted do not all have the full features of FAS. Those with a partial presentation of the features now have a diagnosis that is included within the term Fetal Alcohol Spectrum Disorder (FASD). In all these diagnoses the arenas of diminished growth, facial dysmorphology and brain dysfunction are still the major components of the conditions and are considered as such in each of the commonly used approaches to FASD diagnoses including the Canadian Guidelines for FASD Diagnosis.[2,3,4,5] While there has been some disagreement among the diagnostic approaches on when findings in each of the arenas are deviating sufficiently enough from the mean to be considered abnormal, there is no disagreement that the facial features of FAS including the short PF are the most unique and distinctive components of the FAS phenotype.

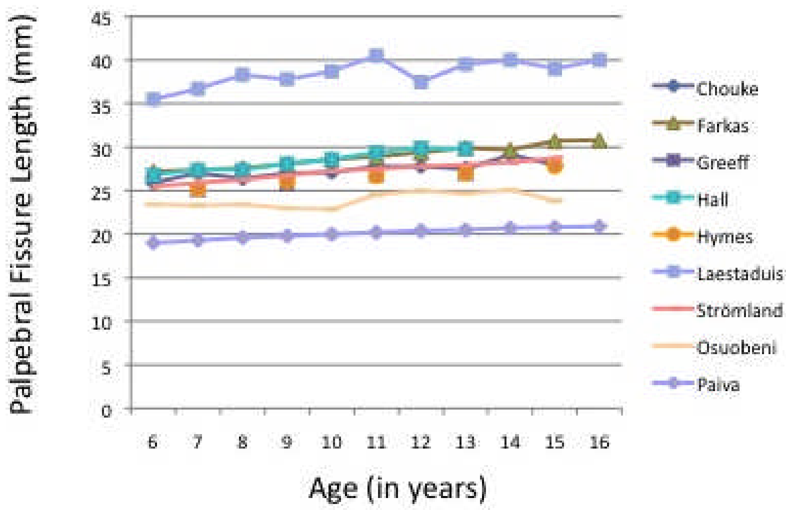
The incidence of FAS in the United States ranges from 1-3 in 1000 live births.[6,7] This value could still very well be an underestimate because of missed or delayed diagnoses.[8] Women are at varying levels of risk for having children with FASD. The risk to each fetus depends on a number of factors including dosage, gestational stage at which alcohol was consumed, as well as maternal and fetal metabolism.[9,10,11,12] It is also possible that some groups may be at higher risk because of unusual customary drinking practices. In one Aboriginal community in British Columbia the prevalence of FAS was determined to be 190 in 1000 children.[13] Accurate incidence and prevalence for FAS/FASD in the general population of Canada have not been established.

Numerous facial abnormalities are seen in children exposed to alcohol and then diagnosed with FAS. These include a short nose, clown eyebrows, midface hypoplasia, retrusive mandible, smooth philtrum, thin upper lip, and short PFs. The findings of the short PFs with a flat philtrum and smooth upper lip have been established as the most critical findings in recognizing the FAS face.[14,15,16,17] While short PFs are characteristic of FAS, they could be seen in a number of other conditions associated with different overall patterns of dysmorphic findings.[18] Because of the centrality of a short PF in making the diagnosis of FAS (and because of its important occurrence in some additional rarer conditions), accurate measurement of the PF and reference to normal values is essential. A set of normative values would allow physicians and other clinicians to provide more prompt and accurate diagnosis.

Previous studies have demonstrated that the length of the PF varies between races and by age and perhaps by gender while the length remains uniform between the left and right eye.[19,20,21,22,23] By the time a child reaches fifteen or sixteen years of age, the length of his/her PFs has generally reached adult size.[24] Past studies of PFs have primarily focused on Caucasians and Blacks in the United States (e.g., Fuchs et al.,[20] Barretto,[25] Jones et al.,[26] and Chouke).[27] In addition, southern Ontario children and adults were studied by Farkas to establish norms that were published in his textbook on anthropometry.[28]

Most people would agree, based on their common experience of looking at others, that PFs seem to be of very similar size from normal person to normal person in any age group with the full normal range spanning only a few millimeters. However, measuring the PF accurately has remained a clinical challenge. Although the length of the PF is defined as the horizontal distance between the endocanthion and the exocanthion the exact landmarks used might be interpreted somewhat differently.[29] Rarely are illustrations provided in publications that show the points that were actually used. Clinical experience also demonstrates that it is necessary to hold the ruler or caliper parallel to the observer and as close to the eye as possible or errors in measurement from parallax will occur. Accuracy to a millimeter is possible with a hand held ruler. Accuracy to a millimeter should be adequate for clinical interpretation of the meaning of the palpebral fissure length. Current published results describe the norm as anywhere between 25mm-30mm in length in any age cohort (e.g., Thomas et al.,[30] Fox,[31] Wolff[32]) while Paiva et al.[33] and Laestadius et al.[19] found more extreme mean values, 18mm and 37mm respectively (Figure 1).

FIG. 1 The wide range of average PF size in different studies is presented for comparison.[19,24,27,33-38]



The problems and possible sources for this impossible incongruity in measurements might lie in how individuals defined the horizontal length of the PF, as well as how the PFs were measured (calipers vs. ruler vs. photographic analysis).[39] Importantly, redundant eyelid tissues like epicanthal folds that obscure the endocanthus and possibly the exocanthus must be gently moved away when measuring the points clinically or a true measure may be somewhat to markedly underestimated. (Unfortunately, it is not possible on photographic analysis to move an epicanthal fold.) Unless the subject voluntarily holds the eye widely open, eyelashes may also obscure the exocanthus. Accuracy may be greatly compromised by guessing where the points are under skin cover or in shadow.

Since it is not morphologically possible that all of the studies of palpebral fissures cited above measured the same thing or measured it accurately, it has not been clear which study or studies should be used for clinical normative reference. Hall et al. did provide a composite graph of PFs based on several studies in the two editions of their book of normal physical measurements[36,40] and clinicians most commonly and broadly use this reference today. Yet in producing the Canadian Guidelines for FASD diagnosis and referencing Hall and the other common references, Chudley, et al.[5] noted the discrepancy in PFs in the various publications and recommended a need to establish updated norms for all ages and subpopulations that would accurately serve the highly heterogeneous population in Canada.

The aim of this study was to establish a set of normative values for palpebral fissure length that reflected growth in school aged groups and encompassed the racial/ethnic/national diversity of Canadian children. These important normative values will aid in the detection of all syndromes that are thought to include short palpebral fissures. More importantly this data is critical to any future efforts at establishing the true prevalence of FAS within the population.

MATERIALS AND METHODS

Study Population

Elementary and secondary schools in Vancouver (2006-2007 academic school year) and Winnipeg (2007-2008 academic school year) were asked to participate. The metropolitan areas of Winnipeg and Vancouver were found to be ideal candidates for this study because the ethnic diversity represented the mosaic genetic culture of Canada as a whole including groups with their origins on all other continents and most Canadian Aboriginal groups, as well – with very few exceptions (such as the Inuit).

Schools were chosen by their neighborhood's ethnic composition. Beginning with secondary schools, postal codes were matched with census data from 2001. By reviewing the Forward Sortation Areas for each school, we were able to compare the ethnic makeup for that region to the ethnic diversity of Canada. Elementary schools that were asked to participate were those that fell within the enrollment boundaries for the desired secondary/middle school.

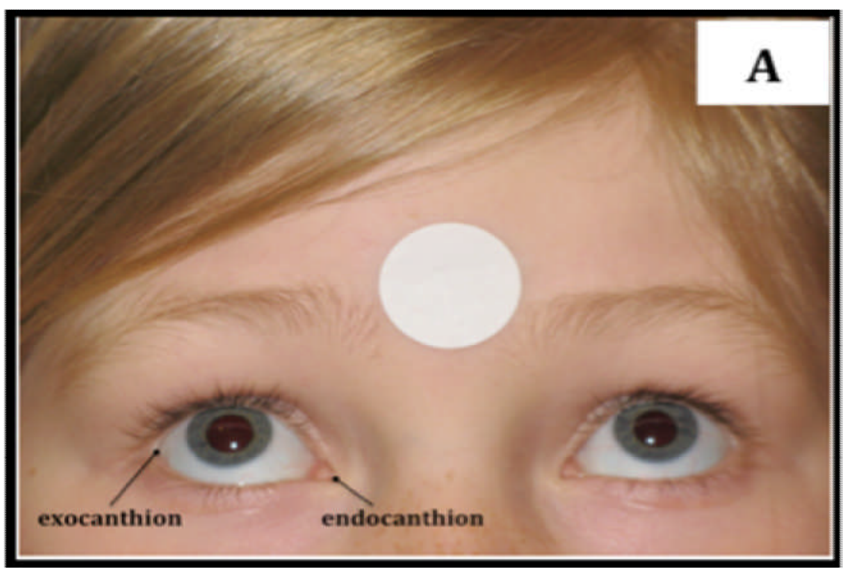
To ensure that a sample with reasonably normal cognition and performance was selected, special education classes were excluded and those students with identified special needs being taught within normal classrooms were permitted to volunteer for a photograph like their classmates but their pictures were excluded from this study.

The study was approved by the Health Research Ethics Board of the Faculty of Medicine at the University of Manitoba and the Behavioural Research Ethics Board at the University of British Columbia. This study received approval from each of the participating School Boards in both cities (Vancouver School Board and the Winnipeg School Division #1), school administrators, and classroom teachers. All students and guardians were provided written information about the study, and those who participated then provided signed consent.

Facial Photo Acquisition

The palpebral fissure lengths were measured from the digital facial photographs using the FAS Facial Photographic Analysis Software.[17] For the purpose of this study the photos captured only the eyes rather than the full face to further protect the identity of the subjects, see Figure 2.

FIG. 2a Photographic region of participants with landmarks identified. This photo was classified as "A" quality.



The pictures were identified only by the sex of the child and a birth date. Ethical consideration prevented the children from identifying themselves by a racial/ethnic group. However, the photographer was able to record which racial category the participant most likely appeared to fall under. After photos of poor quality due to blur or rotation were removed, photographs were sorted into three groups. Group A photos were similar to the one seen in Figure 2a.

The endocanthus and exocanthus were clear. Group B photos had small endocanthal folds so that it seemed possible to trace the angle of the under and lower lids to the endocanthal point accurately (Figure 2b). Group C photos included children with significant epicanthal folds that widely obscured the endocanthus (Figure 2c). Two trained observers measured photos in each group independently. A random sample of twenty photos from Groups A, B, and C were subsequently measured by a third observer to check for measurement variability by group.

FIG. 2b This photo was classified as "B" quality

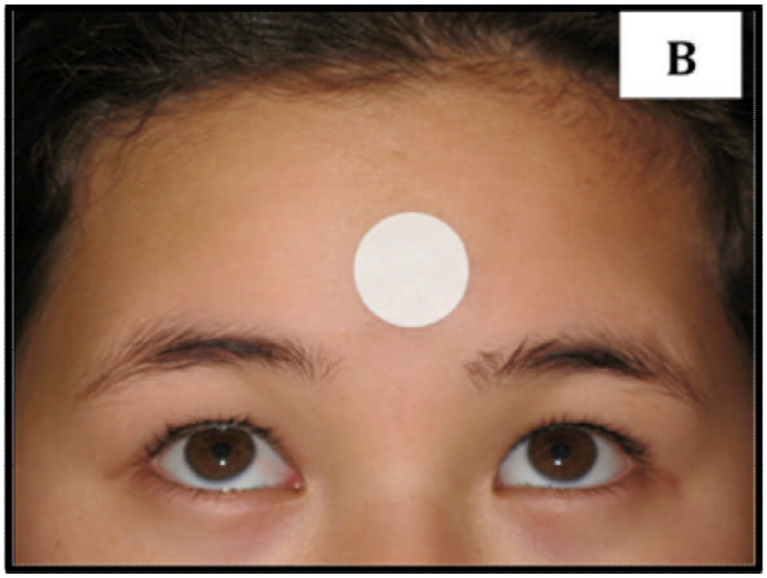
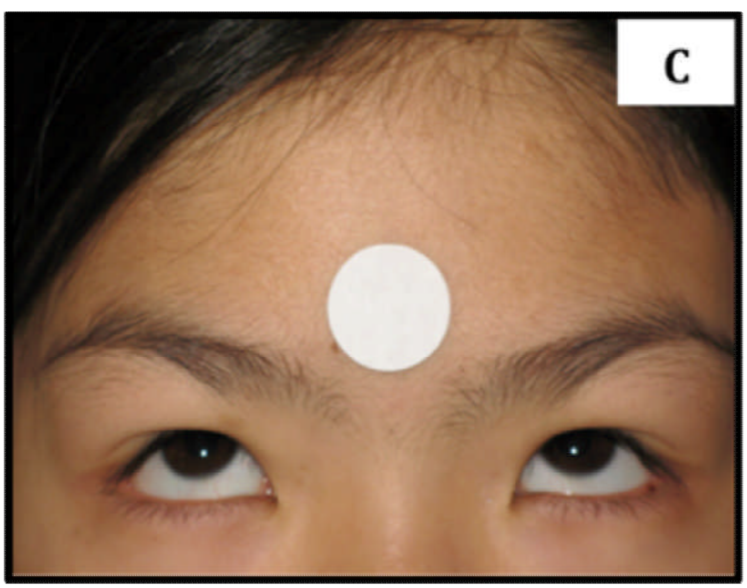


FIG. 2c This photo was classified as "C" quality.



Statistical Analysis
The aim of the analysis was to characterize the distribution of palpebral fissure length in relation to age and sex. Sample size targets of 250 to 500 per two-year age group were chosen so that confidence intervals for tail probabilities would be accurate to within ± 0.015. To estimate percentile curves we applied non-linear quantile regression[41,42,43] to allow for potential non-linearity in age trends and non-normality in the age and sex stratified distribution of PFs. Children over 17 years in age were omitted from the model due to small numbers.

Significant effects of age, sex, and ethnicity were discovered in the initial analysis. Residual analysis indicated that the normal distribution provided an adequate fit to the data, so the model was refit using generalized least squares regression incorporating non-linear trends in mean and variance by sex and age. Ethnicity was omitted from the final model, as the estimated effects were not deemed to be of sufficient magnitude to warrant construction of ethnic-specific curves.

RESULTS

Final participants included in the analysis were between the ages of 6-17 years. Seventeen schools in Vancouver participated in the study of which 14 were elementary schools (K-7) and 3 secondary schools (grades 8-12). Conversely, 31 schools in Winnipeg took part, 15 elementary schools, 11 middle schools, and 5 high schools. In total, 2097 students from Vancouver and Winnipeg had their photos included in the final analysis. Forty-three percent of the participants were male compared to the 57% female, Table 1.

TABLE 1 Participant Demographic Characteristics (N = 2097)

Characteristic	N (%)
Gender	
Male	903 (43.1)
Female	1194 (56.9)
Ethnicity	
Caucasian	1069 (51.0)
Asian	636 (30.3)
South Asian	68 (3.2)
Southeast Asian	127 (6.1)
Aboriginal	90 (4.3)
Black	53 (2.5)
Others	54 (2.6)

The inter-class correlation coefficient for inter-observer reliability was .73 in Group A photos and .68 in Group B. The frequency of photographs as classified by their quality is presented in Table 2. Gender and age patterns for photographs that were in Group A or B were analyzed separately revealing similar patterns of relationship, and, most importantly, similar residual standard deviations, indicating comparable quality of fit for the two groups. The two groups were therefore combined for the final analysis. Because of the ethical constraints of the project, we could only measure racial/ethnic status from appearance. We were not able to ask the subjects nor their families about mixed racial background nor the location of the participating families of origin. Thus, participants representing various broad Canadian sub-populations were combined. The assumed ethnic breakdown of the participants is presented in Table 1. Some specific Canadian First Nations are underrepresented and the Inuit were largely absent from this study.

TABLE 2 Frequency of Photograph Quality by Ethnicity

	Photograph Quality – N (%)		
	A	**B**	**C**
Caucasian	912 (85.0)	157 (14.6)	4 (0.4)
Asian	162 (24.4)	474 (71.3)	29 (4.4)
South Asian	63 (92.6)	5 (7.4)	0 (0.0)
Southeast Asian	31 (24.4)	96 (75.6)	0 (0.0)
Aboriginal	58 (62.4)	32 (34.4)	3 (3.2)
Black	46 (86.8)	7 (13.2)	0 (0.0)
Other	42 (76.4)	12 (21.8)	1 (1.8)

Our results agree with all past studies in confirming that PFs grow with age until the later part of adolescence and that boys have somewhat larger palpebral fissures at all ages. The estimated mean difference in millimeters between PF for boys and girls was 0.48 (95% C.I. 0.36 to 0.60, P <.0001). Though apparently small we chose to develop separate graphs because use of a common graph would give rise to detection rates in girls nearly twice that of boys. Slight differences were also found between the Vancouver sample and the Winnipeg sample. These differences were generally 1 millimeter or less and so were not deemed to be relevant for clinical work since these differences were smaller than the clinical ability to measure accurately with a hand held ruler.

Additionally, it was found that children who appeared principally to be Black or South Asian had palpebral fissures that were slightly longer than those children thought to be White or Aboriginal Canadian and these were in turn slightly longer than children thought to be Asian. However, the differences again were less than a millimeter and thus so small as not to be clinically significant. Furthermore, the children who were found to be at the lowest percentiles within each age group sample were not an oversample of the Asian populations. The PF results are found in Figures 3a-d.

FIG. 3a Presenting Canadian norms for girl's age 6 to 16 years with cut-offs.

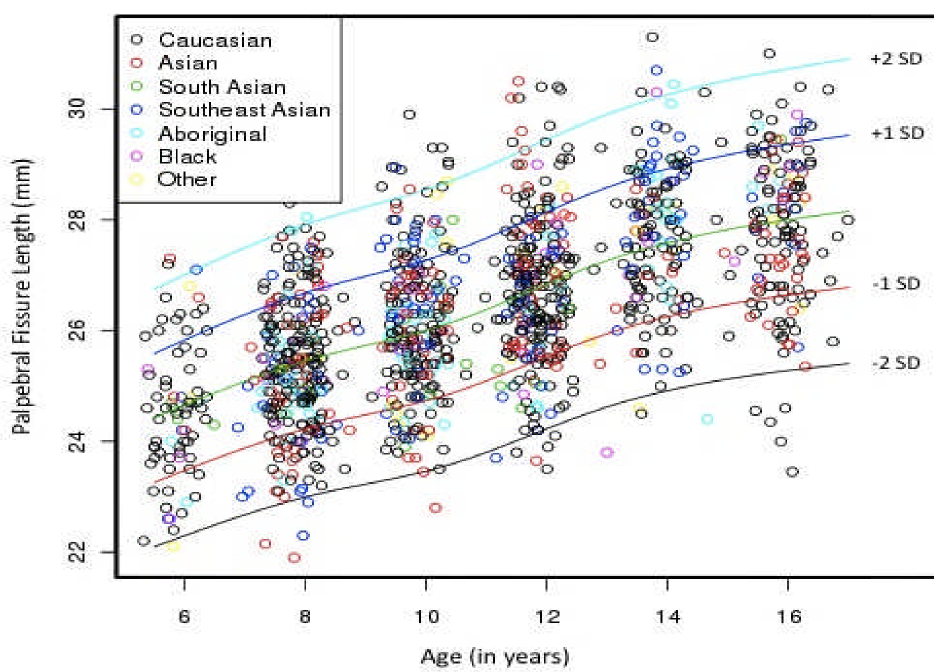


FIG. 3b Presenting Canadian norms for boy's age 6 to 16 years with cut-offs.

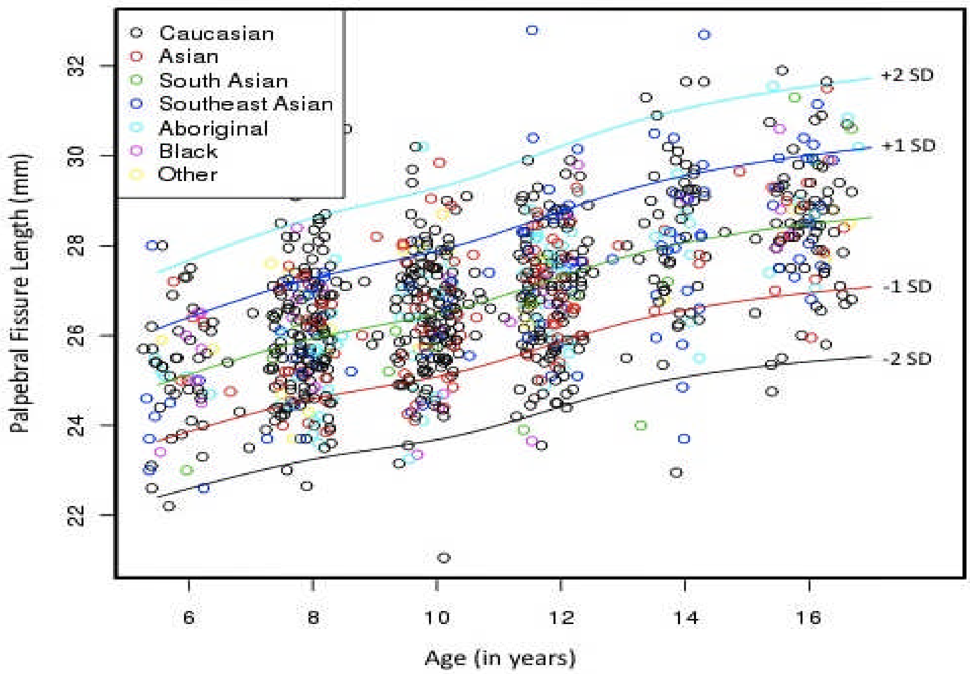


FIG. 3c Presenting Canadian norms (mean and SD) for girl's age 6 to 16 years.

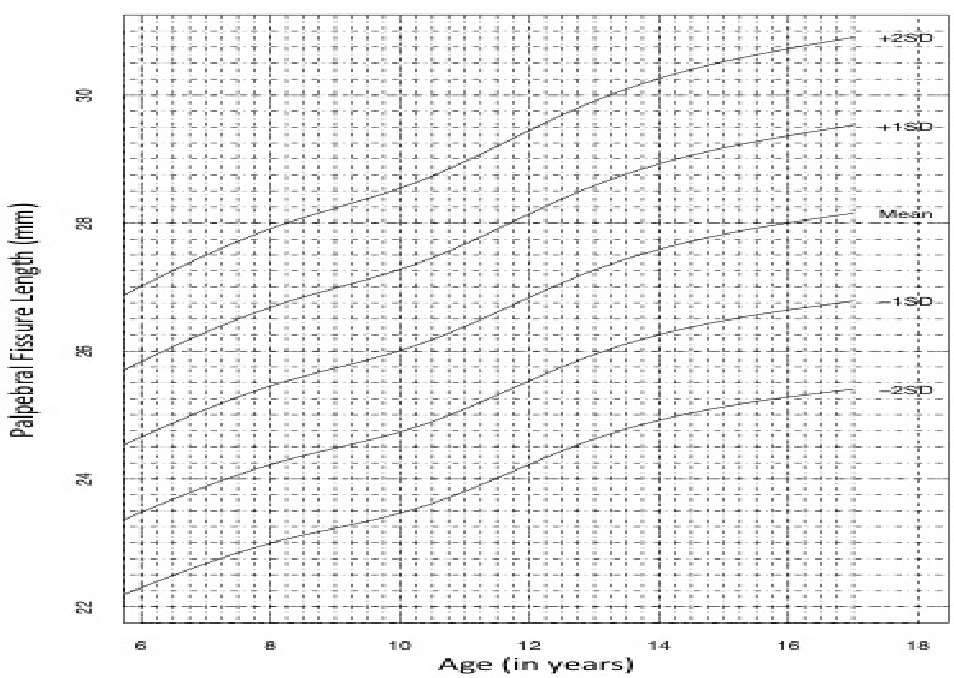
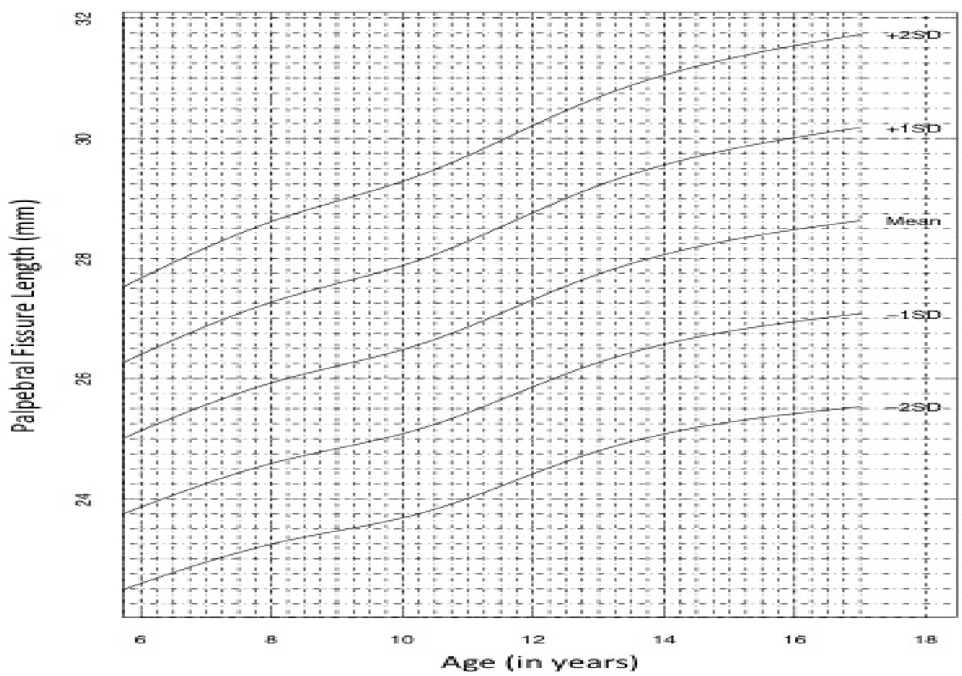


FIG. 3d Presenting Canadian norms (mean and SD) for boy's age 6 to 16 years.

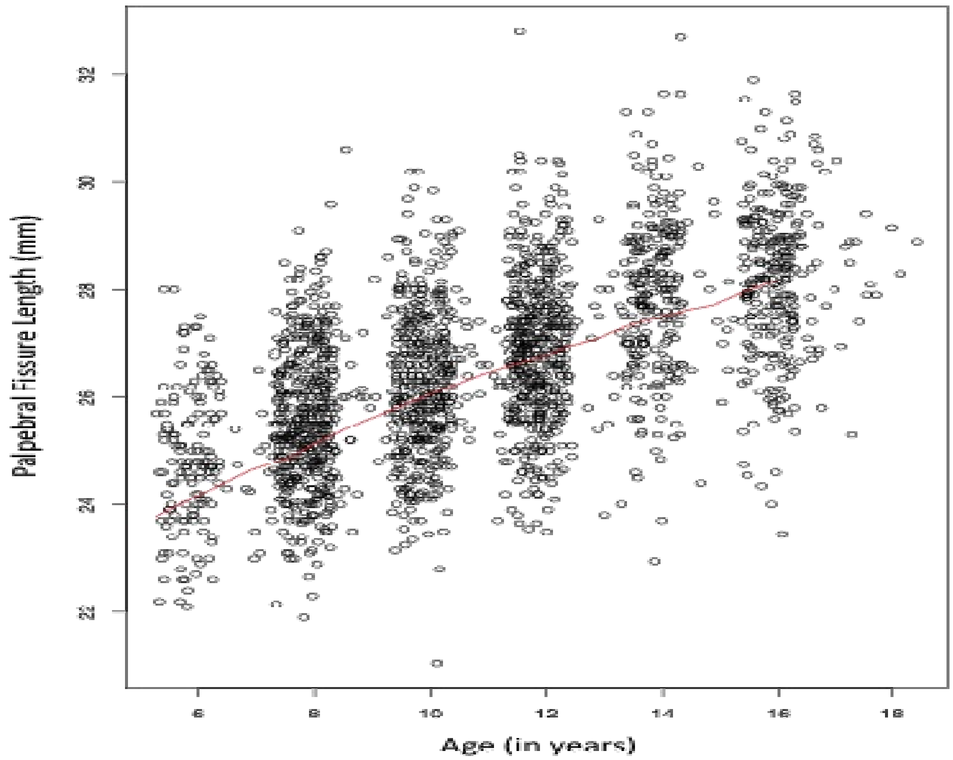


DISCUSSION

To our knowledge, this study is one of the largest and most comprehensive attempts at a population based measure of normal palpebral fissures across school age children and the first in Canada. The work is not without limitations. Ethnicity was self-reported in the census and may not aptly reflect the community sampled. Moreover, measurements were difficult to obtain from pictures of participants with prominent epicanthal folds, which resulted in photographs being excluded from the analysis. Lastly, while the research team was able to obtain a representative sample of most sub-populations one important Canadian population, the Inuit, were definitely under sampled. However, given the commonality in PF size across all other racial and ethnic groups, it is likely that these charts can be fair used in subsequent studies in Canadian Northern populations as well as elsewhere. The results are at odds with the commonly used chart available in Hall et al.[36] Forty percent of the children in this study would have been measured as below minus two standard deviations on the Hall chart (Figure 4). That chart was derived from a combination of results from multiple studies that were individually wide ranging in their values. Further, it has been difficult to mathematically reproduce the mean results of the Hall graph suggesting perhaps, a reproductive error in placing the curves accurately on the printed background grid.

Based on the size of this study, the rigor and accuracy in the method of measurement and the tight agreement between observers, we believe that these data can be used as a single standard for all school age children assessed for palpebral fissures in Canada and could be used most likely in other locations as well.

FIG. 4 Children in this study who's PFs would fall below -2 SD on the chart in the *Handbook of Normal Physical Measurements* by Hall et al.[36]



Acknowledgements
The research team would like to thank the Vancouver School Board, the Winnipeg School Division #1, school administrators, teachers, and the families of children that participated in this study. The Canada Northwest FASD Research Network and the Child and Family Research Institute provided administrative and funding support.

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REFERENCES

1. Sokol RJ, Clarren SK. Guidelines for use of terminology describing the impact of prenatal alcohol on the offspring. Alcoholism Clinical and Experimental Research 1989;13:597-598.
2. Stratton KR, Howe CJ, Battaglia FC. Fetal Alcohol Syndrome: diagnosis, epidemiology, prevention and treatment. Washington, DC: Institute of Medicine, National Academy Press, 1996.
3. Astley SJ, Clarren SK. Diagnosing the full spectrum of fetal alcohol exposed individuals: introducing the 4-digit diagnostic code. Alcohol 2000;35:400-410.
4. 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. Pediatr 2005;115:39-47.
5. Chudley AE, Conry J, Cook JL, Loock C, Rosales T, LeBlanc N. Fetal alcohol spectrum disorder. Canadian guidelines for diagnosis. CMAJ 2005;172:S1-S21.
6. 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.
7. May PA, Gossage JP, Kalberg WO, et al. Prevalence and epidemiologic characteristics of FASD from various research methods with emphasis on recent in-school studies. Developmental Disabilities Research Reviews 2009;15:176-192.

8. Sokol RJ, Delaney-Black V, Nordstrom B. Fetal alcohol spectrum disorder. JAMA 2003;290(22):2996-2999.
9. Ernhart CB, Sokol RJ, Martier S, et al. Alcohol teratogenicity in the human: a detailed assessment of specificity, critical period, and threshold. American Journal of Obstetrics & Gynecology 1987;156(1):33-39.
10. Clarren SK, Bowden DM, Astley SJ. Pregnancy outcomes after weekly oral administration of ethanol during gestation in the pig-tailed macaque (Macaca nemestrina). Teratology 1987;35:345-354.
11. Roccella M, Testa D. Fetal Alcohol Syndrome in developmental age. Minerva Pediatrica 2003;55:63-74.
12. Chambers CD, Hughes S, Meltzer SB, et al. Alcohol consumption among low-income pregnant Latinas. Alcoholism: Clinical and Experimental Research 2005;29(11):2022-2028.
13. 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.
14. Clarren SK, Sampson PD, Larsen J, et al. Facial effects of fetal alcohol exposure: assessment by photographs and morphometric analysis. American Journal of Medical Genetics 1987;26:651-666.
15. Sokol RJ, Chik L, Martier SS, Salari V. Morphometry of the neonatal fetal alcohol syndrome face from ‘snapshots.’ Alcohol & Alcoholism 1991;Supp. 1:531-534.
16. Lewis DD, Woods SE. Fetal Alcohol Syndrome. American Family Physician 1994;50(5):1025-1032.
17. Astley SJ. FAS Facial Photographic Analysis Software. Version 1.0.0, 2003. University of Washington, Seattle WA.
18. Dooling EC, Oppenheimer EY, Kayne H, et al. Width of the palpebral fissure in newborn infants: another measure of neural growth. Annals of Neurology 1982;12(2):217.[Abstract]
19. Laestadius MD, Aase JM, Smith DW. Normal inner canthal and outer orbital dimensions. The Journal of Pediatrics 1969;74(3):465-468.
20. Fuchs M, Iosub S, Bingol N, Gromisch DS. Palpebral fissure size revisited. Journal of Pediatrics 1980;96(1):77-78.
21. Leung AKC, Ma KCH, Siu TO, Robson WLM. In Chinese Newborn Infants: Comparison with Other Ethnic Groups. Clinical Pediatrics 1990;29(3):172-174.
22. Hajnis K, Farkas LG, Nagim RCK, Lee ST, Venkatadri G. Racial and ethnic morphometric differences in the craniofacial complex. In: Farkas LE, ed. Anthropometry of the Head and Face. 2nd ed. New York: Raven Press, 1994:201-218.
23. Douglas TS, Viljoen DL. Eye measurements in 7 year old Black South African children. Annals of Human Biology 2006;33(2):241-254.
24. Hymes C. The postnatal growth of cornea and palpebral fissure and the projection of the eyeball in early life. The Journal of Comparative Neurology 1929;48:415-440.
25. Barretto RL, Mathog RH. Orbital measurement in Black and White populations. Laryngoscope 1999;109(7):1051-1054.
26. Jones KL, Hanson JW, Smith DW. Palpebral fissure size in newborn infants. Pediatr 1978;92(5):787.
27. Chouke KS. The epicanthus or Mongolian fold in Caucasian children. American Journal of Physical Anthropology 1929;13(2):255-279.
28. Farkas LG. Anthropometry of the Head and Face (2nd edition). New York: Raven Press, 1994:103–111.
29. Souza ADA, Ruiz EES, Cruz AAV. Palpebral fissure morphology segmentation using image processing. IEEE Engineering in Medicine and Biology 2000;19(1):114-119.
30. Thomas I, Gaitantzis Y, and Frias J. Palpebral fissure length from 29 weeks gestation to 14 years. The Journal of Pediatrics 1987; 111(2):267-268.
31. Fox SA. The Palpebral Fissure. American Journal of Ophthalmology 1966;62(1):73-78.
32. Wolff E. Anatomy of the eye and orbit (7th edition). Philadelphia: WB Saunders, 1976:183.
33. Paiva RSN, Minare-Filho AM, Abenor M. Palpebral Fissure Changes in Early Childhood. Journal of Pediatric Ophthalmology and Strabismus 2001;38(4):219-223.
34. Farkas LG. Anthropometry of the Head and Face in Medicine. New York: Elsevier, 1981.
35. Greeff R. Studien ueber die Plastik des menschlichen Auges am Lebenden und an den Bildwerken der Antike. Anat. Abt. Arch. Anat. Physiol. Zugleich Arch. Anat. Entwicklungsgesch 1892;113–135.
36. Hall J, Froster-Iskenius U, Allanson J. Handbook of Normal Physical Measurements. New York: Oxford University Press, 1989;150.
37. Strömland K, Chen YH, Norberg T, Wennerstrom K, Michael G. Reference values of facial features in Scandinavian

children measured with a range-camera technique. Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery 1999;33:59–6.

38. Osuobeni EP, Al Musa KA. Gender differences in interpupillary distance among Arabs. Optometry and Vision Science 1993;70:1027–1030.
39. Cranston ME, Mhanni AA, Marles SL, Chudley AE. Concordance of three methods for palpebral fissure length measurement in the assessment of fetal alcohol spectrum disorder. Fetal Alcohol Research in Canadian Journal of Clinical Pharmacology 2009;16(1): e234-41.
40. Hall J, Allanson J, Gripp KW, Slavotinek AM. Handbook of Normal Physical Measurements. New York: Oxford University Press, 2007;132.
41. Koenker R, Ng P, Portnoy S. Quantile Smoothing. Splinesâ Biometrika 1994;81:673-680.
42. Koenker R. (2006). quantreg: Quantile Regression. R package version 4.05. http://www.r-project.org.
43. R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2006, ISBN 3-900051-07-0, Available online: http://www.R-project.org.