

Asymmetry-index and orthodontic facial analysis of children with fetal alcohol syndrome (FAS) using 3D-facial scans

Cite this article as: Moritz Blanck-Lubarsch, Dieter Dirksen, Reinhold Feldmann, Cristina Sauerland, Christian Kirschneck and Ariane Hohoff, Asymmetry-index and orthodontic facial analysis of children with fetal alcohol syndrome (FAS) using 3D-facial scans, *Pediatric Research* doi:10.1038/s41390-019-0559-5

This Author Accepted Manuscript is a PDF file of an unedited peer-reviewed manuscript that has been accepted for publication but has not been copyedited or corrected. The official version of record that is published in the journal is kept up to date and so may therefore differ from this version.

Terms of use and reuse: academic research for non-commercial purposes, see here for full terms. <https://www.nature.com/authors/policies/license.html#AAMtermsV1>

Author accepted manuscript

Asymmetry-index and orthodontic facial analysis of children with fetal alcohol syndrome (FAS) using 3D-facial scans

Moritz Blanck-Lubarsch^{a,§}, Dieter Dirksen^b, Reinhold Feldmann^c, Cristina Sauerland^d, Christian Kirschneck^e, Ariane Hohoff^a

^aDepartment of Orthodontics, University of Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany

^bDepartment of Prosthodontics and Biomaterials, University of Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany

^cDepartment of Pediatrics, University of Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany

^dInstitute of Biostatistics and Clinical Research, University of Münster, Schmeddingstraße 56, 48149 Münster, Germany

^eDepartment of Orthodontics, University of Regensburg, Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany

[§]Corresponding author, Department of Orthodontics, University of Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany, phone: +49 251 83-47100, fax: +49 251 83-47187, e-mail address: blancklubarsch@uni-muenster.de

Authors' contributions

AH and MBL suggested the original idea for the paper. AH, MBL and DD developed the study design and wrote the study protocol. MBL collected the data, did the literature research and wrote the main part of the manuscript. RF recruited the children and verified/negated FAS diagnoses for each child. CS performed the statistical analysis. CS and CK contributed to the interpretation of the results. DD and CK contributed to the statistical analysis and data handling and revised the manuscript. All authors reviewed the paper for content and read and approved the final manuscript. All of them agree to be accountable for all aspects of the work

in enduring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Statement of financial support

No financial assistance was received in support of this study.

Disclosure

The authors declare no conflict of interest.

Category of study

Clinical research study

ABSTRACT

Objective

The fetal alcohol spectrum disorder (FASD) is a complex and heterogenic disorder, caused by gestational exposure to alcohol. Patients with fetal alcohol syndrome (FAS – most severe form) show abnormal facial features. Our study aims at finding additional reliable and objective parameters for FAS diagnosis.

Methods

Facial 3D scans of 30 children with FAS and 30 controls were analysed. Orthodontic profile analysis (concerning position of upper and lower jaw) was performed. Vertical facial proportions were taken and facial asymmetry index (right to left side) was calculated.

Results

Profile type was significantly different for children with FAS ($p=0.001$) with lower jaws more frequently in a retral position. Profile angle was significantly larger in the group with FAS ($p=0.009$). Children with FAS had shorter middle thirds and longer lower thirds of the face ($p<0.001$). Stomion (point between upper and lower lip) was located significantly more caudally in the FAS group ($p<0.001$). Facial asymmetry index was not significantly different.

Conclusions

Children with FAS differ significantly from controls in vertical and sagittal facial measurements. Profile analysis and measurement of vertical proportions are easy to apply standard procedures in everyday orthodontic practice and could be time-saving and objective means for additional verification of FAS.

Introduction

The fetal alcohol spectrum disorder (FASD), which is caused by alcohol consumption during pregnancy, is a developmental disorder with lifetime consequences for the affected person entailing high costs for the public health care systems (1, 2). In different studies the prevalence of FASD shows variation depending on ethnic or geographic origin, age of the study population and differing study designs (3-5). According to Lange et al., the worldwide estimated prevalence for FASD is 0.77% with regional differences ranging from 1.98% in Europe to 0.01% in the eastern Mediterranean region (6). A study analyzing the prevalence of FASD in a UK population found a prevalence of 6 to 7.2 % (7). The prevalence of FASD in Canadian school children was estimated to be between 2 to 3 % (8). Another study by May et al. found a prevalence of 1.1 to 5 % in first grade school children in the United States (9). The term fetal alcohol syndrome (FAS) was first coined by Jones and Smith in 1973, but descriptions of FASD-related symptoms reach back even further (10, 11).

FASD as a generic term comprises all severity grades of FASD symptoms such as fetal alcohol syndrome (FAS) with or without confirmed alcoholic exposure during pregnancy, partial fetal alcohol syndrome (pFAS), alcohol-related birth defects (ARBD) or alcohol-related neurodevelopmental disorder (ARND) (12). A recent Canadian study by Popova et al. found an estimated prevalence of 1.2 per 1000 for FAS, 2.0 per 1000 for pFAS and 15 per 1000 for ARND for school children aged 7-9 years (8). Due to the complexity and heterogeneity of FASD, achieving a reliable diagnosis is challenging. The existing variability of diagnostic methods concerning FASD impedes comparability and reproducibility (13). So far the 4-digit diagnostic code, introduced by Astley is the most standardized diagnostic tool available (1, 14-17). The diagnostic code consists of four components including growth deficiency, facial phenotype, central nervous system (CNS) damage or dysfunction as well as

gestational exposure to alcohol (15, 17). For facial phenotyping in FASD diagnostics a commonly used diagnostic tool is the lip philtrum guide by Astley and Clarren (<https://depts.washington.edu/fasdpn/htmls/lip-philtrum-guides.htm>).

All currently available diagnostic means for FASD, however, are partially based on visual evaluation of facial features. For this reason, it is essential for the improvement of FASD diagnosis that objectively measurable facial aberrations can be detected and quantified. Optical 3D scanning methods are non-invasive, riskless, fast and comfortable for the patient and allow objective metric measurements of facial structures (18), based on an accurate and reliable identification of anatomical landmarks of the face (19). Various methods describing the degree of facial symmetry either from two-dimensional or three-dimensional data have been presented (20, 21).

2D photography and its analysis is already a standardized method in orthodontic diagnosis and treatment planning. Established orthodontic analyses were thus used in the current study and transferred to 3D images of the face. According to A. M. Schwarz, nine different variations of facial profile can be distinguished (22). These are categorized as protrusive, retrusive and normal according to the position of the point Subnasale (Sn) in relation to a vertical line perpendicular to the Frankfort horizontal plane running through the soft tissue Nasion (N). Each of these categories is then subdivided in "askew to the back", "askew to the front" or "straight" depending on the position of pogonion within the so-called "jaw profile area" (22). According to Fang et al. facial proportional analysis reaches back as far as to the Greek neoclassical canons (450 B.C.) (23). In 1886 Kollmann described a vertical subdivision of the face into equal thirds (24). The measurement of these proportions according to Kollmann is commonly used for the orthodontic analysis of facial profile pictures.

Symmetry of the face is an important aspect of facial analysis for evaluation of malocclusions

in the transverse dimension and evaluation of the attractiveness of a face. FASD is diagnosed by evaluation of facial parameters. It therefore seems interesting to investigate possible facial asymmetries in patients with FAS (most severe form of FASD). Asymmetry can be determined using a facial asymmetry index, which is calculated using a vertical reference line and measuring individual symmetry values for pairs of points (20).

The aim of our study was to assess differences in facial morphology of children with FAS - being the most severe form of the spectrum of FASD - as compared to normal controls and to find new reliable, objective parameters for improvement of FAS diagnosis based on non-invasive diagnostic 3D scans of the face.

METHODS

Study design, setting and participants

Data acquisition for our prospective observational cross-sectional study took place in the time period between 2012 and 2016. A total of 30 Caucasian children with FAS (mean age 8.8 years; range 6.6-11.2 years; 15 male and 15 female) and 30 healthy controls (mean age 8.2; range 5.8-11.9 years; 18 male and 12 female) were examined in the Department of Orthodontics of the University Hospital Muenster. Recruitment of the included children with FAS was done in cooperation with the Department of Pediatrics of the University Hospital Muenster. A pediatric specialist verified or negated FAS diagnosis for each child or the healthy controls, respectively, according to the German FAS diagnostic guideline (1). For a valid diagnosis of FAS all of the following criteria had to apply: growth deficiency, facial phenotype, central nervous system damage or dysfunction and gestational exposure to alcohol. Patients with less severe forms of FASD such as partial FAS, ARBD or ARND were excluded from our investigation.

The control group consisted of voluntary children from local schools. Exclusion criteria for both groups were former or present orthodontic treatment, deciduous or permanent dentition and any previous or present disease, trauma, surgical intervention, disorder or syndrome affecting the facial contour.

Variables and data sources/management

The optical 3D facial scans were contact-free and based on the fringe projection technique. The head of the sitting patient, positioned at a defined distance from the scanner was adjusted according to the Frankfort horizontal and the pupillary planes parallelised to the ground horizontal with the aid of a light projection. A LCD projector (VT 58, NEC) projected a sequence of binary and sinusoidal vertical stripes onto the face, which were recorded by three charge coupled device (CCD) cameras (Imagingsource GmbH, Bremen, Germany – outer cameras monochrome, inner camera Bayer-type colour sensor) on a horizontal track with a digital interface (IEEE1394) and a resolution of 1024 x 768 pixels (25). Within approximately one second a point cloud consisting of 50.000 to 800.000 facial 3D coordinates was rendered per patient. Using the software pVision3D, which was developed by the Department of Prosthodontics and Biomaterials of the University Hospital of Muenster, the facial surface was then reconstructed as a triangle mesh by connecting the individual coordinate points via Delaunay triangulation (26) with the colour image of the central camera used for texturing (18).

Based on the reconstructed 3D facial data, the following outcome parameters were assessed:

- 1) facial and profile type as well as profile angle according to A.M. Schwarz, 2) facial proportions according to Kollmann, 3) lower facial proportions according to A.M. Schwarz and 4) the facial asymmetry index (AI) (22, 24, 27).

The analysis of the facial and profile type was done according to the established 2D analysis by A.M. Schwarz in profile view of the face (Figure 1) (22, 27). The facial type is determined by drawing a perpendicular line (Perpendiculare nasale, Pn) to the Frankfort Horizontal (FH) through Nasion (N). Depending on the position of the Subnasale (Sn) to Pn, a protrusive, normal or retrusive facial type is diagnosed. A second perpendicular line (Perpendiculare orbitale, Po) is drawn to the FH through Orbitale (O) in order to determine the profile type. The area between the two perpendicular lines Pn and Po is called “jaw profile area” (Kieferprofilfeld) (22, 27). The position of the chin (Pogonion, Pog) is used to diagnose profile type as straight, askew to the front or askew to the back. The profile angle is defined as the angle between the tangent Sn to Pog and the Pn line with an average value of 10 degrees (27).

The analysis of vertical facial proportions (thirds) was carried out in frontal view according to Kollmann (Figure 2). The middle third was measured from Glabella (G) to Subnasale (Sn) and the lower third from the Subnasale (Sn) to Menton (Me), with each section parallel to the bipupillary line. The upper third was not evaluated because of possible bias concerning the positioning of the Trichion (Tr) at the hairline, since Tr is often difficult to localise depending on hair configuration (24, 28). An up to 10% larger lower facial third compared to the middle third is considered to be within the normal range (27). We thus calculated the ratio of lower to middle facial third with the normal range from 0.9 to 1.1 (27).

The lower facial third was further analysed concerning the position of Stomion (Sto) in order to evaluate the length of the upper lip (Figure 2). The quotient ratio of the linear distances Sn to Sto and Sto to Me was determined. A value of 0.5 is defined to be normal, a value of > 0.5

shows a caudal position of Stomion, and a value of < 0.5 shows a cranial position.

The software gView3D was used to calculate the facial asymmetry index (AI). For this purpose, a mirrored (at the median sagittal plane) copy of the facial surface is calculated and matched to the original surface using iterative closest point algorithm. The average distance d_a between the two facial surfaces was calculated. The result was then divided by the diagonal B_d of the smallest cuboid enclosing the face (“Bounding Box”). To obtain more easily readable numbers in a single-digit range, the resulting value was then multiplied by 1000:

$$AI = \frac{d_a}{B_d} \times 1000 \quad (21).$$

The division of the two length values results in a dimensionless number.

The higher the asymmetry index (AI) the more asymmetric is the face (Figure 3).

Heat maps/ Thin plate splines

For the purpose of visualization of aberrant facial features in patients with FAS we used heat maps. Facial profile and en face landmarks were identified from 3D coordinates. The resulting coordinates were then scaled using Procrustes fitting. Heat maps were created using the Thin plate spline function (Figure 4).

Bias

To minimize bias, controls were recruited from local schools instead of an orthodontic university department to avoid selection of extreme malocclusions and oral phenotypes, which could have a potential influence on facial contour. All study participants were screened based on a standardized orthodontic examination protocol and all scans and measurements were performed by the same experienced orthodontist. All data were blinded regarding study groups prior to measurements and statistical evaluation. Since children with FAS show retarded development, we chose to include slightly (but not statistically significant) younger

patients as controls in order to optimize comparability (29-31). The included children were therefore similar concerning parameters like body length or weight.

Statistical analysis

All analyses were performed with the software IBM® SPSS® Statistics 24 (IBM, Armonk, NY). Categorical variables were described by absolute frequencies. Metric variables were characterised by the arithmetic mean (M), standard deviation (SD), median (MD) and range (minimum, maximum). Due to violations of requirements for parametrical testing, Mann-Whitney-U tests were used to assess differences between FAS and control groups, whereas Fisher's exact test was employed to compare FAS versus control groups for all categorical variables. All analyses were regarded as explorative and p-values interpreted descriptively. Primary endpoints of the study are: facial type, profile type, Kollmann's proportion, lower facial third and asymmetry index. An adjustment for multiple testing for example using the Bonferroni method ($\alpha/5$) does not change the results. Therefore, no adjustment for multiple testing was performed. The local two-sided significance level was set at 5%. Multivariate analyses were performed for prognostic variables using logistic regression analysis including the following variables: gender, profile angle, Kollmann's proportion, lower facial third. P-values from these analyses were based on Wald-test.

Ethical approval

The study was approved by the ethics committee of the medical association of Westphalia – Lippe and the Department of Medicine, University of Münster, Germany, study-code 2012-196-f-S. The investigation was performed in compliance with the current revision of the Declaration of Helsinki, and with the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines. Written informed consent for performing the 3D

scans, data analysis and publication of associated results was obtained beforehand from all patients and their legal guardians.

RESULTS

Study participants

30 children (15 female, 15 male) with FAS und 30 controls (12 female and 18 male) were examined. The FAS group had an average age of 8.8 years (SD 1.4), the controls were on average 8.2 years (SD 1.8) old (Table 1). There were no significant differences between the two groups with respect to gender distribution ($p=0.604$) or age ($p=0.099$) (Table 1).

Main results

Profile type

Concerning the profile type, a significantly different distribution ($p=0.001$) could be found. The measurements for profile type were significantly different for gender specific comparison as well (females: $p=0.024$ and males: $p=0.046$). The mean profile angle was significantly different between the groups ($p=0.009$) and larger for FAS children ($20.9 \pm 4.1^\circ$) compared to the controls ($17.8 \pm 4.4^\circ$). For female patients, profile angle was not significantly different ($p=0.139$) as compared to males with $p=0.044$. Two patients in the FAS group had straight profiles and 28 patients had profiles that were askew to the back. By contrast, 13 faces in the control group were straight and 17 askew to the back (Table 1). None of the patients in both groups had a profile that was askew to the front.

Facial proportions

The comparison of both groups regarding facial proportions showed highly significant differences ($p<0.001$). Gender specific comparison showed significant differences for females with $p=0.009$ and males with $p=0.015$. A highly significant difference ($p<0.001$) could also be

found concerning the lower third with $p=0.040$ for females and $p<0.001$ for males. The frequency of children with a shorter middle facial third was higher in the FAS group ($n=24$) than in the control group ($n=9$) (Table 1). A normal facial subdivision was only found in four FAS and 14 control children. A shorter lower or longer middle third could be found in two FAS and seven control children (Table 1). Only three children of the FAS group had a normal lower third (vs. 21 controls). The point Stomion was located more caudally in 21 of the FAS patients (vs. 3 control patients). Only few patients had a cranial position of the point Stomion (6 FAS patients vs. 6 controls).

Facial type

No statistically significant difference was observed between groups concerning the distribution of facial types ($p=0.898$) with the normal facial profile found in 10 children with FAS and 12 controls. A retrusive facial type could be found in 9 FAS and 8 control children and 11 FAS versus 10 controls had a protrusive facial type (Table 1). The same applies for gender specific comparison with $p=0.332$ for females and $p=0.749$ for males.

Asymmetry Index

The asymmetry index (AI) did not significantly differ between the two groups (FAS 2.5 ± 1.5 ; controls 2.7 ± 1.2). No significant gender specific differences could be found ($p=0.227$ for males and $p=0.767$ for females).

Sensitivity and specificity

Using the analysed parameters (gender, profile angle, Kollmann's proportions, lower facial third) 86.7 % of the FAS patients can be diagnosed correctly. The specificity is 93.3 %. (Fig. 5).

DISCUSSION

The diagnostic process in FASD patients is difficult and based in parts on subjective parameters (13). Recent studies by Valentine et al. 2017 and Suttie et al. 2013 suggest that

computer based facial recognition may be suitable in discriminating facial feature of less severe forms of FASD (such as pFAS or ARND) from healthy controls (32, 33). For this reason, we set out to investigate possible differences in facial morphology of children with FAS compared to normal controls to find additional and more objective parameters for FAS verification. Further studies in patients with less severe forms of FASD could investigate possible transferability of the specific diagnostic facial parameters.

Suttie et al. used heat maps to highlight facial dysmorphisms in FAS patients (33-35). We performed heat map visualizations of our FAS patients in comparison with controls as well (Figure 4). The Thin plate splines enable visualization of the underdeveloped areas in the chin and eye region (blue colours) as well as vertical enlargement in the philtrum area (red colours). However, this method is in our opinion not suitable for everyday clinical use, which is why we used orthodontic facial analysis methods to simplify diagnosis.

Two-dimensional facial analyses are standardized and easy to apply methods in everyday orthodontic treatment planning. Using these measuring methods can therefore give additional hints for abnormal facial features. 3D-scans as basis for the 2D-facial measurements of profile analysis have the advantage of higher accuracy (31).

Our study could show that facial type and vertical facial proportions differ significantly in FAS children compared with healthy controls. Facial symmetry, however, does not seem to be influenced by gestational alcohol exposure, since the asymmetry index did not differ significantly, when comparing FAS children with the healthy controls. In contrast, a study by Klingenberg et al. compared patients with FAS and a control group and did find a significant difference in directional asymmetry of the face (36). To our understanding the method used in their study was Procrustes fit with 17 evaluated landmarks, which were positioned manually with an accuracy of two millimeters per linear measurement. In comparison, the strength of

our study is that we used a three-dimensionally scanned point cloud of 50.000 to 800.000 points, which provided extremely accurate calculations concerning the asymmetry index. In addition, the diagnosis of FAS was based on different diagnostic guidelines.

FAS children more frequently had profiles that were askew to the back than the controls. This fact hints at sagittal deficiencies in the mandibular area. A small or retrusive mandible has been described by Clarren et al., who used a triangle shape connecting nasion, gnathion and upper lip for analysis (37).

In addition, in our study the profile angle was significantly larger in the FAS group, which is in accordance with the sagittal deviations we found in these children. For the profile angle, gender specific differences could be detected in our study, since comparison of female patients showed non-significant results ($p=0.139$) for females as compared to significant differences for males ($p=0.044$).

The vertical middle facial third was more frequently shorter in the FAS group. A recent study from Blanck-Lubarsch et al. detected a transversal underdevelopment of the maxilla which matches the found vertical deficiency in this area (38). For the lower third a significant difference could be found with the FAS patients having more frequently longer lower thirds than the controls.

The Stomion was positioned more frequently in a caudal position, which could be due to a more vertical or longer upper lip in FAS patients. Since diagnosis of FAS(D) is in parts based on the evaluation of philtrum depth (39) the aberrant position of Stomion could give additional hints in the diagnostic process.

These findings show that vertical and sagittal facial proportions and profiles differ significantly between FAS and healthy control patients. According to available studies concerning patients with FAS features such as hypoplastic midface, smooth philtrum or short palpebral fissure length can be used for diagnosis (40). Using orthodontic facial analysis as described in our study can additionally help objectifying FAS diagnosis. Using the analysed parameters (gender, profile angle, Kollmann's proportions, lower facial third) 86.7 % of the FAS patients can be diagnosed correctly and the specificity is 93.3 %. (Figure 5). This is in accordance with similar results found by Valentine et al. for computer-aided diagnosis in patients with FASD (32). Our calculated values for sensitivity and specificity underline the potential helpfulness of using the presented measurements in combination with 3D technology in patients with FAS.

In addition, orthodontic facial analysis is easy to apply and can therefore easily be adapted in everyday clinical practice. In our study, only patients with FAS as the most severe form of FASD were included. More measurements of facial structures should be taken in order to find possible further abnormal values, which could support and facilitate FAS diagnostics in the future. In addition, it is necessary to find more methods for the diagnosis of patients with less severe forms of FASD such as partial FAS where not all criteria of the guidelines apply. 3D-scans could in the future facilitate and standardize the diagnostic process with all the facial features being available in just one scan within a short period of time (approximately one second). With available databases of specific values or percentile curves for FAS(D) facial features this could be a helpful addition for everyday practice.

At present, a limitation could be the availability of scanning devices. However, with further technical advancement 3D-scanning devices become more and more popular for use in private practices as well as in clinics.

CONCLUSION

FAS children showed significant differences in facial profile and proportions. Particularly sagittal deficiencies could be found in children with FAS with respect to profile, which was more frequently askew to the back. Also in the vertical dimension, significant aberrations from normal facial proportions could be found with the middle facial third being more frequently shorter and the lower third being longer in FAS children. Asymmetry does not seem to be a relevant parameter for diagnosis.

The applied facial measurements for facial profile and proportions are suitable additional parameters for FAS verification. Further studies should analyse a possible transferability for the diagnosis of patients with less obvious clinical features as in partial FAS or ARND. Our results could therefore support diagnostic procedures for patients with FAS by providing additional objective parameters for FAS verification.

Ethical approval

The study was approved by the ethics committee of the medical association of Westphalia – Lippe and the Department of Medicine, University of Münster, Germany, study-code 2012-196-f-S. The investigation was performed in compliance with the current revision of the Declaration of Helsinki, and with the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines. Written informed consent for performing the 3D scans, data analysis and publication of associated results was obtained beforehand from all patients and their legal guardians.

REFERENCES

1. Landgraf MN, Nothacker M, Heinen F Diagnosis of fetal alcohol syndrome (FAS): German guideline version 2013. *Eur J Paediatr Neurol.* (2013)
2. Lupton C, Burd L, Harwood R Cost of fetal alcohol spectrum disorders. *Am J Med Genet C Semin Med Genet* 127C:42-50. (2004)
3. May PA, de Vries MM, Marais AS, et al. The continuum of fetal alcohol spectrum disorders in four rural communities in South Africa: Prevalence and characteristics. *Drug Alcohol Depend* 159:207-218. (2016)
4. May PA, Marais AS, de Vries MM, et al. The continuum of fetal alcohol spectrum disorders in a community in South Africa: Prevalence and characteristics in a fifth sample. *Drug Alcohol Depend* 168:274-286. (2016)
5. Roozen S, Peters GJ, Kok G, Townend D, Nijhuis J, Curfs L Worldwide Prevalence of Fetal Alcohol Spectrum Disorders: A Systematic Literature Review Including Meta-Analysis. *Alcohol Clin Exp Res* 40:18-32. (2016)
6. Lange S, Probst C, Gmel G, Rehm J, Burd L, Popova S Global Prevalence of Fetal Alcohol Spectrum Disorder Among Children and Youth: A Systematic Review and Meta-analysis. *JAMA Pediatr* 171:948-956. (2017)
7. McQuire C, Mukherjee R, Hurt L, et al. Screening prevalence of fetal alcohol spectrum disorders in a region of the United Kingdom: A population-based birth-cohort study. *Prev Med* 118:344-351. (2019)

8. Popova S, Lange S, Chudley AE, Reynolds JN, Rehm J World Health Organization International Study on the Prevalence of Fetal Alcohol Spectrum Disorder (FASD). (2018)
9. May PA, Chambers CD, Kalberg WO, et al. Prevalence of Fetal Alcohol Spectrum Disorders in 4 US Communities. *JAMA* 319:474-482. (2018)
10. Jones KL, Smith DW Recognition of the fetal alcohol syndrome in early infancy. *Lancet* 302:999-1001. (1973)
11. Lemoine P, Harousseau H, Borteyru JP, Menuet JC Children of Alcoholic Parents - Anomalies in 127 Cases. *Archives Francaises De Pediatrie* 25:830-+. (1968)
12. May PA, Baete A, Russo J, et al. Prevalence and characteristics of fetal alcohol spectrum disorders. *Pediatrics* 134:855-866. (2014)
13. Coles CD, Gailey AR, Mulle JG, Kable JA, Lynch ME, Jones KL A Comparison Among 5 Methods for the Clinical Diagnosis of Fetal Alcohol Spectrum Disorders. *Alcohol Clin Exp Res* 40:1000-1009. (2016)
14. Astley SJ, Clarren SK Diagnosing the full spectrum of fetal alcohol-exposed individuals: introducing the 4-digit diagnostic code. *Alcohol Alcohol* 35:400-410. (2000)
15. Clarren SK, Chudley AE, Wong L, Friesen J, Brant R Normal distribution of palpebral fissure lengths in Canadian school age children. *Can J Clin Pharmacol* 17:e67-78. (2010)
16. Hoyme HE, May PA, Kalberg WO, et al. A practical clinical approach to diagnosis of

fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. *Pediatrics* 115:39-47. (2005)

17. Hoyme HE, Kalberg WO, Elliott AJ, et al. Updated Clinical Guidelines for Diagnosing Fetal Alcohol Spectrum Disorders. *Pediatrics* 138. (2016)

18. Bischoff G, Borocz Z, Proll C, Kleinheinz J, von Bally G, Dirksen D Modular optical topometric sensor for 3D acquisition of human body surfaces and long-term monitoring of variations. *Biomed Tech (Berl)* 52:284-289. (2007)

19. Lippold C, Liu X, Wangdo K, et al. Facial landmark localization by curvature maps and profile analysis. *Head Face Med* 10:54. (2014)

20. Berlin NF, Berssenbrugge P, Runte C, et al. Quantification of facial asymmetry by 2D analysis - A comparison of recent approaches. *J Craniomaxillofac Surg* 42:265-271. (2014)

21. Berssenbrugge P, Berlin NF, Kebeck G, et al. 2D and 3D analysis methods of facial asymmetry in comparison. *J Craniomaxillofac Surg* 42:e327-334. (2014)

22. Schwarz AM Gebisswinkel und Profil. *Deutsche Zahn-, Mund- und Kieferh.* 2:487. (1935)

23. Fang F, Clapham PJ, Chung KC A systematic review of interethnic variability in facial dimensions. *Plast Reconstr Surg* 127:874-881. (2011)

24. Kollmann J *Plastische Anatomie des menschlichen Körpers für Künstler und*

Freunde der Kunst. Veit&Comp, Leipzig. (1886)

25. Berssenbrugge P, Lingemann-Koch M, Abeler A, et al. Measuring facial symmetry: a perception-based approach using 3D shape and color. *Biomed Tech (Berl)* 60:39-47. (2015)
26. de Berg M, Cheong O, van Kreveld M, Overmars M *Computational Geometry: Algorithms and Applications*. Springer Berlin Heidelberg. (2008)
27. Schwarz AM *Roentgenostatics: A practical evaluation of the x-ray headplate*. *American Journal of Orthodontics* 47:561-585. (1961)
28. Fink M, Medelnik J, Strobel K, Hirschfelder U, Hofmann E Metric precision via soft-tissue landmarks in three-dimensional structured-light scans of human faces. *J Orofac Orthop* 75:133-143. (2014)
29. Carter RC, Jacobson JL, Sokol RJ, Avison MJ, Jacobson SW Fetal alcohol-related growth restriction from birth through young adulthood and moderating effects of maternal prepregnancy weight. *Alcohol Clin Exp Res* 37:452-462. (2013)
30. Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, Young JK Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. *J Dev Behav Pediatr* 25:228-238. (2004)
31. Fink M, Hirschfelder U, Hirschinger V, et al. Assessment of facial soft-tissue profiles based on lateral photographs versus three-dimensional face scans. *J Orofac Orthop* 78:70-76. (2017)

32. Valentine M, Bihm DCJ, Wolf L, et al. Computer-Aided Recognition of Facial Attributes for Fetal Alcohol Spectrum Disorders. *Pediatrics* 140. (2017)
33. Suttie M, Foroud T, Wetherill L, et al. Facial dysmorphism across the fetal alcohol spectrum. *Pediatrics* 131:e779-788. (2013)
34. Suttie M, Wetherill L, Jacobson SW, et al. Facial Curvature Detects and Explicates Ethnic Differences in Effects of Prenatal Alcohol Exposure. *Alcohol Clin Exp Res* 41:1471-1483. (2017)
35. Suttie M, Wozniak JR, Parnell SE, et al. Combined Face-Brain Morphology and Associated Neurocognitive Correlates in Fetal Alcohol Spectrum Disorders. *Alcohol Clin Exp Res* 42:1769-1782. (2018)
36. Klingenberg CP, Wetherill L, Rogers J, et al. Prenatal alcohol exposure alters the patterns of facial asymmetry. *Alcohol* 44:649-657. (2010)
37. Clarren SK, Sampson PD, Larsen J, et al. Facial effects of fetal alcohol exposure: assessment by photographs and morphometric analysis. *Am J Med Genet* 26:651-666. (1987)
38. Blanck-Lubarsch M, Flieger S, Feldmann R, Kirschneck C, Sauerland C, Hohoff A. Malocclusion Can Give Additional Hints for Diagnosis of Fetal Alcohol Spectrum Disorder. *Alcohol Alcohol*. (2018)
39. Blanck-Lubarsch M, Dirksen D, Feldmann R, Sauerland C, Kirschneck C, Hohoff A. 3D Analysis of Philtrum Depth in Children with Fetal Alcohol Syndrome. *Alcohol Alcohol*.

(2019)

40. Astley SJ, Clarren SK A fetal alcohol syndrome screening tool. *Alcohol Clin Exp Res* 19:1565-1571. (1995)

Figure 1 Facial and profile analysis according to A.M. Schwarz. Normal facial type with a profile askew to the back. Perpendiculare nasale (Pn) and Perpendiculare orbitale (Po) create the “jaw profile area” (Kieferprofilfeld). Pn and Po are constructed perpendicular to the Frankfort horizontal (FH) through Nasion (N) and Orbitale (Or), respectively. The profile angle is measured between Pn and the line connecting Subnasale (Sn) and Pogonion (Pog).

Figure 2 Facial proportions according to Kollmann (parallel to the bipupillary line (Bp)). The upper facial third is located between Trichion (Tr) and Glabella (Gl), the middle third between Gl and Subnasale (Sn) and the lower third between Sn and Menton (Me). The lower third can be subdivided according to A.M. Schwarz by Stomion (Sto) into an upper third and two lower thirds.

Figure 3 Assessment of facial asymmetry. *Left:* calculated symmetry plane (blue), bounding box (light red) and the diagonal B_d (red) ; *Right:* depiction of the symmetry plane (central orange line) with distances between the mirrored point clouds depicted as pseudocolours. Minimal distances (symmetric areas) shown as light blue and maximum distances (most asymmetric areas) shown in yellow.

Figure 4 Heat maps/ Thin plate splines

Visualization of aberrant facial features in FAS. Blue areas showing compression, red areas showing expansion. a) Thin plate spline of profile picture. Blue colour in mandible region supporting the finding that the mandible was askew to the back. Red colour showing caudal position of stomion and greater philtrum length. b) Thin plate spline of en face picture. Blue areas in chin and eye region showing underdevelopment. Red colour in upper lip and nose region showing caudal position of stomion as well as greater length of upper lip.

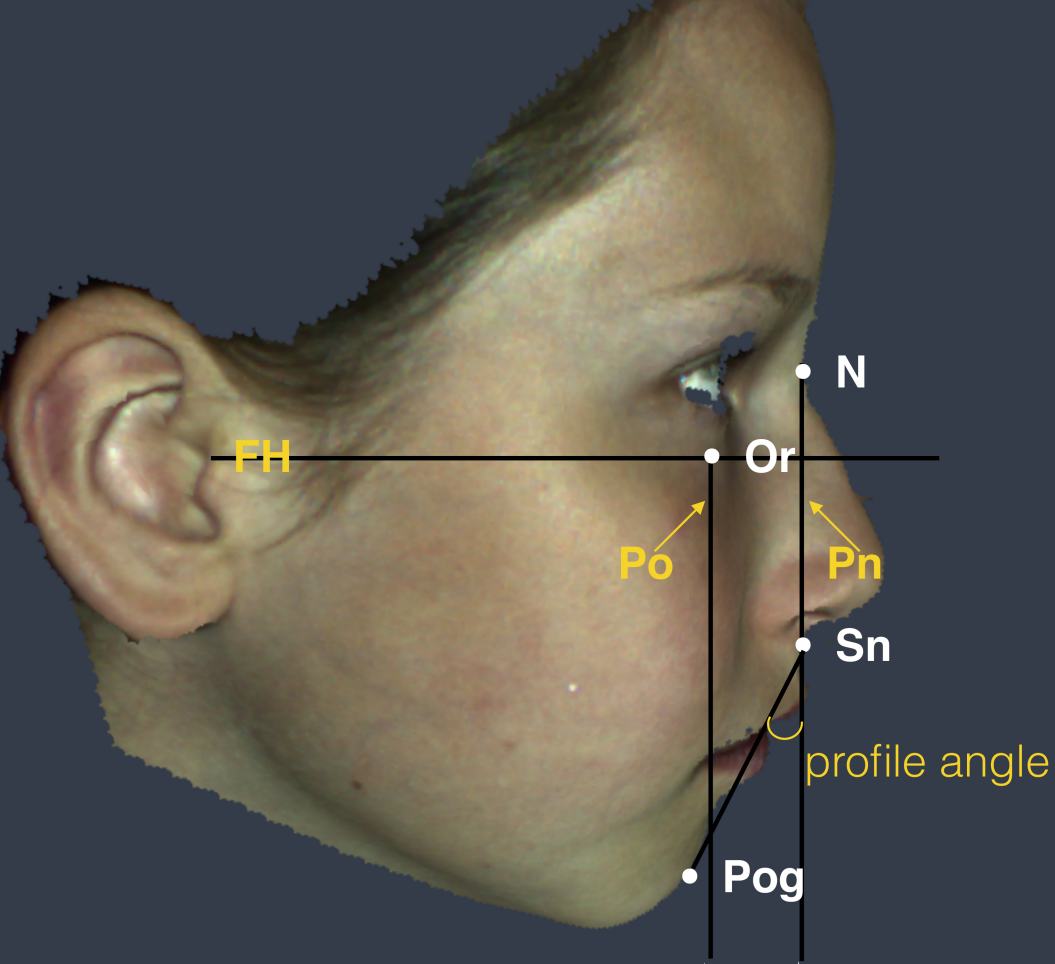
Figure 5 ROC curve

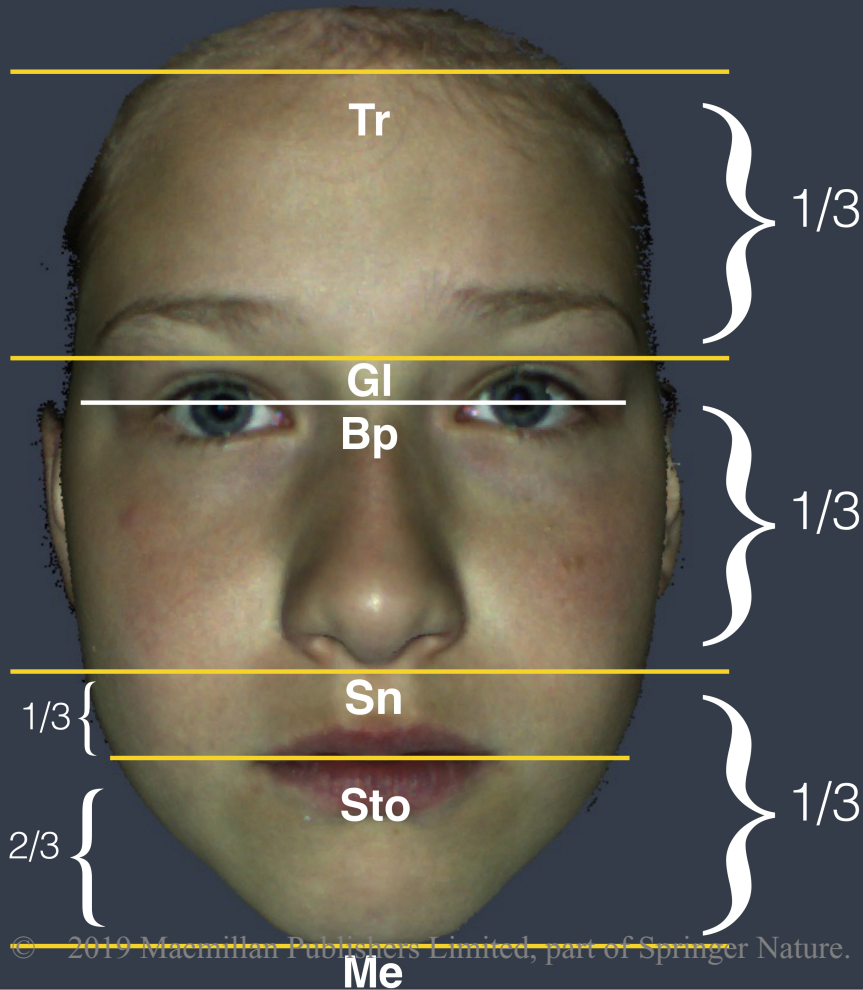
Using the analysed parameters (gender, Profile angle, Kollmann's proportion, lower facial third) 86,7 % of the FAS patients can be diagnosed correctly.

Table 1 Descriptive and analytical statistics for all outcome parameters evaluated

	Total	FASD-group	c-group	P value
Gender				0.604**
male	33	15	18	
female	27	15	12	
Age at examination, years				0.099*
Mean (SD)	8.5 (1.6)	8.8 (1.4)	8.2 (1.8)	
Median (Range)	8.3 (5.8-11.9)	8.6 (6.6-11.2)	7.6 (5.8-11.9)	
Weight at examination, kg				0.468*
Mean (SD)	28.3 (6.5)	27.9 (6.8)	28.7 (6.3)	
Median (Range)	27.3 (18.5-45.8)	26.5 (20-45.8)	28.3 (18.5-39)	
Height at examination, cm				0.579*
Mean (SD)	131.5 (11.5)	130.9 (10.5)	132.2 (12.6)	
Median (Range)	130.6 (110-164)	128.5 (113-161)	132.7 (110-164)	
Head circumference at examination, cm				<0.001*
Mean (SD)	51.4 (2.3)	50.2 (2.4)	52.6 (1.4)	
Median (Range)	51.9 (46-55)	50.5 (46-54)	52.7 (50-55)	
Facial type				0.898**
normal	22	10	12	
retrusive	17	9	8	
protrusive	21	11	10	
Profile type				0.001**
straight	15	2	13	
askew to the front	0	0	0	
askew to the back	45	28	17	
Profile angle				0.009*
Mean (SD)	19.4 (4.5)	20.9 (4.1)	17.8 (4.4)	
Median (Range)	19.4 (10.3-28.6)	20.2 (11.7-28.6)	17.4 (10.3-26.2)	
Kollmann's proportion				<0.001**
normal subdivison	18	4	14	
shorter middle third / longer lower third	33	24	9	
longer middle third / shorter lower third	9	2	7	
Lower facial third				<0.001**
normal	24	3	21	
caudal position of stomion	24	21	3	
cranial position of stomion	12	6	6	
Asymmetry index				0.148*
Mean (SD)	2.6 (1.3)	2.5 (1.5)	2.7 (1.2)	
Median (Range)	2.1 (1.1-7.8)	2.0 (1.1-7.8)	2.3 (1.6-5.7)	

* Mann-Whitney-U test; ** Fisher's exact test.





Tr

1/3

Gl

Bp

1/3

Sn

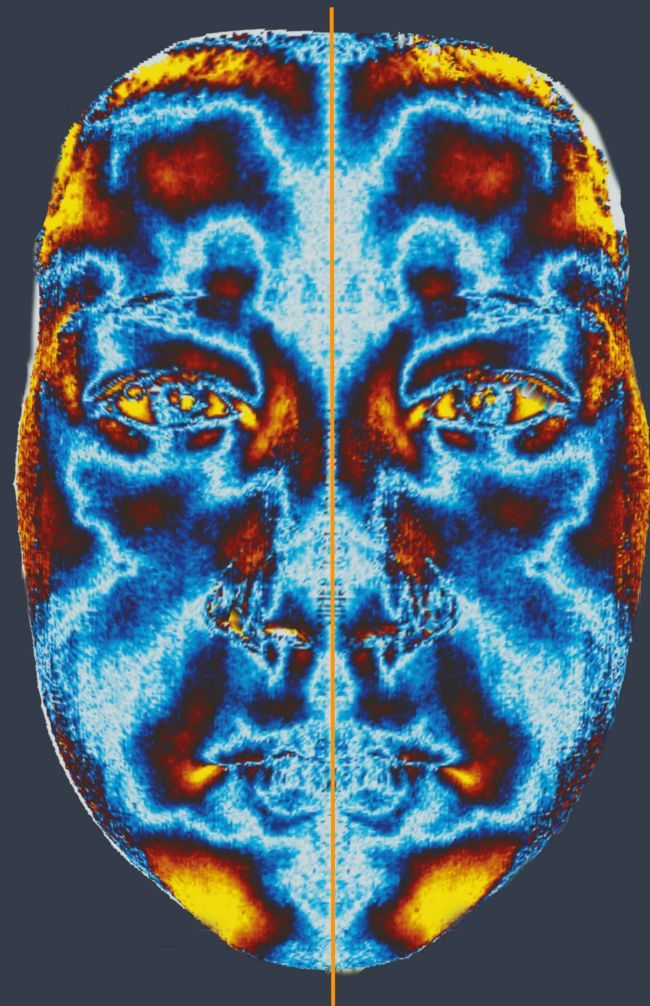
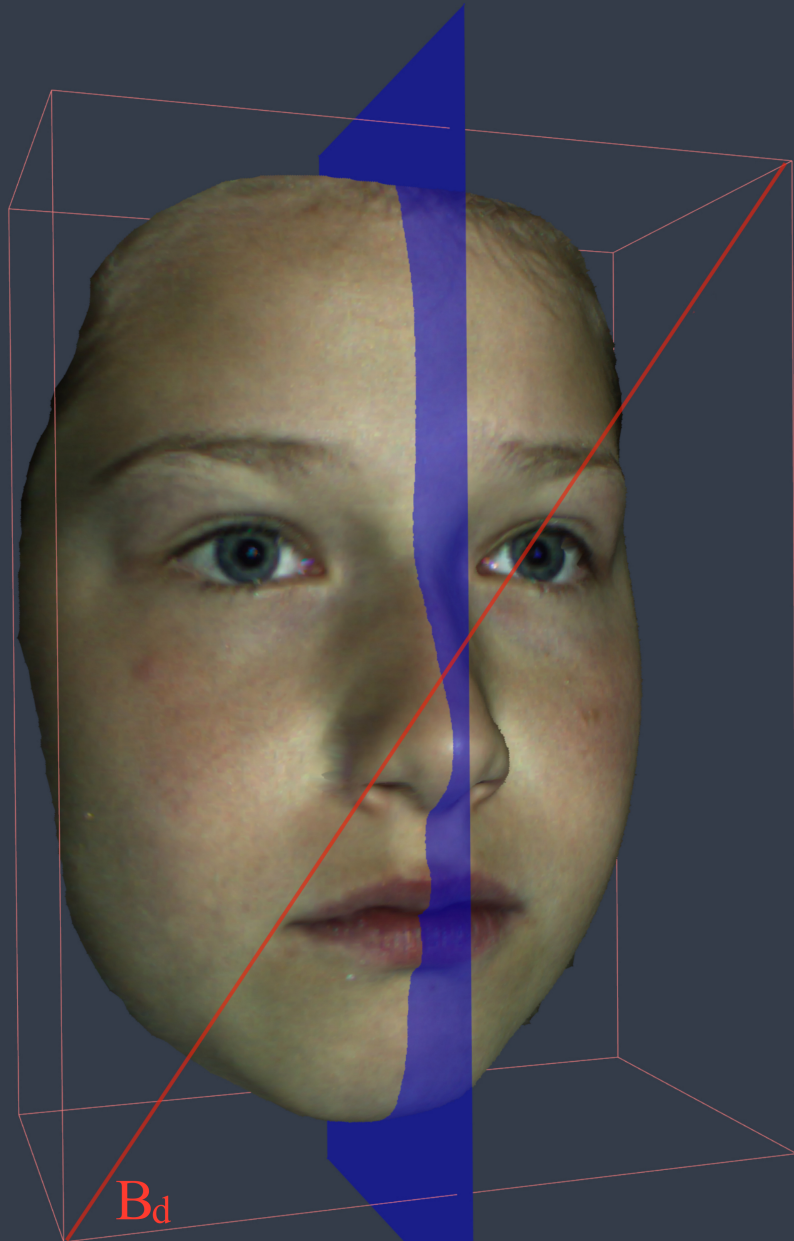
1/3

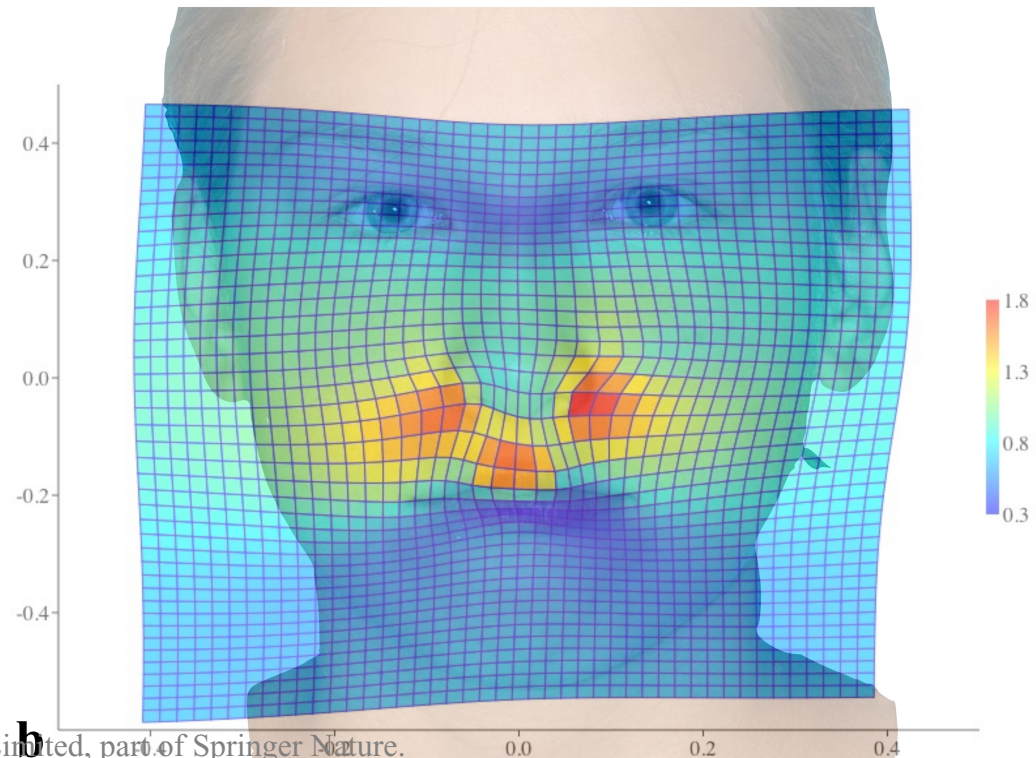
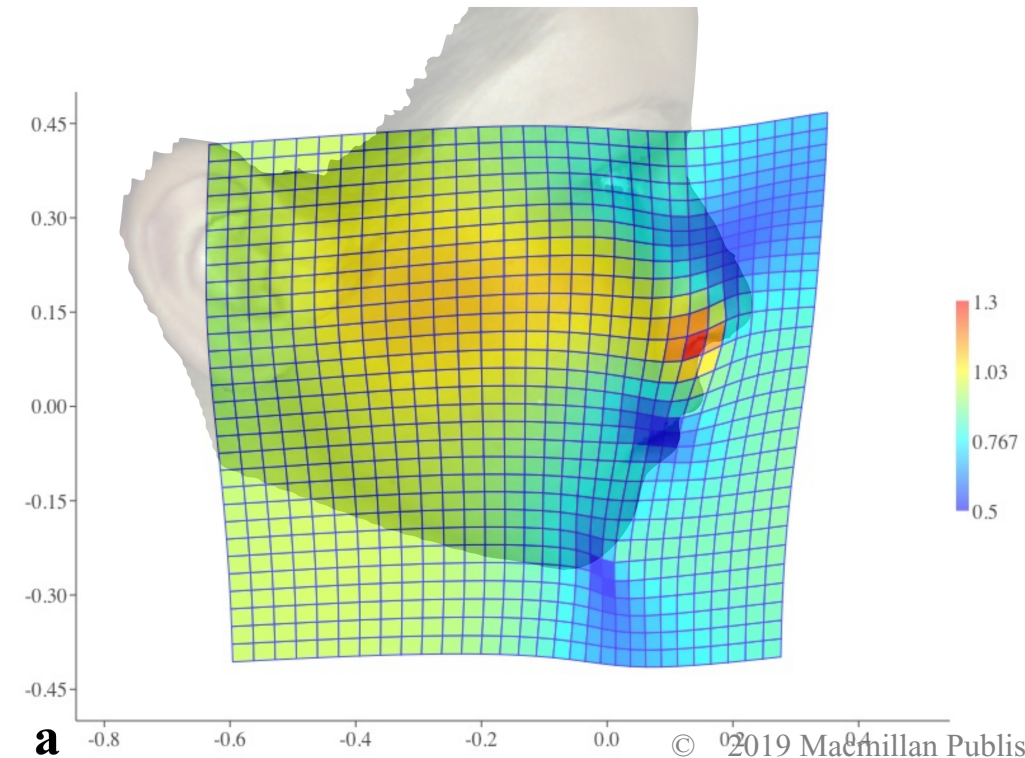
Sto

1/3

Me

2/3



**a****b**

ROC Curve FAS versus Control

