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Fetal Alcohol Spectrum Disorders from Childhood to Adulthood: A Population Based Naturalistic Cohort Study

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Abbreviations:

ABAS-II = Adaptive Behavior Assessment Scale II

ADHD = Attention Deficit Hyperactivity Disorder

ARBD = Alcohol-Related Birth Defect

ARND = Alcohol-Related Neurodevelopmental Disorder

BMI = Body Mass Index

BP = Blood Pressure

CGI-S = Clinical Global Impression-Severity scale

DCD = Developmental Coordination Disorder

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition

ICD = Inner Canthal Distance

IQ = Intelligence Quotient

MINI = Mini International Neuropsychiatric Interview 6.0.0

OFC = Occipitofrontal Circumference

PFAS = Partial Fetal Alcohol Syndrome

PFL = Palpebral Fissure Length

Word count: 3286 words.

Abstract

Background

Fetal Alcohol Spectrum Disorders (FASD) are a global health concern. To further understand the adult outcome of FASD is a major public health interest.

Objective

To characterize the adult outcome of fetal alcohol spectrum disorders (FASD) in children adopted to a socially favorable and stable rearing environment.

Design

Prospective observational cohort study

Setting

Western Sweden

Participants

From a population-based cohort study of carefully examined adoptees, thirty-seven individuals diagnosed with FASD in childhood were approached for follow-up as young adults.

Outcome measures

Assessment consisted of up to three follow-up evaluations of social, medical, psychiatric, neuropsychological, adaptive, and ophthalmological status.

Results

Out of 37 adoptees with FASD, 36 (15 females) were evaluated at a median age of 22 (18–28) years and a mean follow-up time of 15.5 years. Twenty (56%) were dependent on social support. Sexual victimization was reported by nine (26%). In 21 individuals with fetal alcohol syndrome, growth restriction in height and head circumference of approximately -1.8 standard deviations persisted into adulthood. Of 32 examined, 22 (69%) had gross motor coordination abnormalities. High blood pressure was measured in nine (28%). Ophthalmological abnormalities were found in 29 of 30 (97%). A median IQ of 86 in childhood had declined significantly to 71 by adulthood (mean difference: 15.5; 95% confidence interval 9.5–21.4). Psychiatric disorders were diagnosed in 88%, most commonly attention deficit hyperactivity disorder (70%). Three or more disorders were diagnosed in 48%, and 22% had attempted suicide. The median Clinical Global Impression-Severity score was 6 = “severely ill.”

Conclusion

Major cognitive impairments, psychiatric morbidity, facial dysmorphology, growth restriction and ophthalmological abnormalities accompanies FASD in adulthood. Recognition of FASD in childhood warrants habilitation across the lifespan.

Article Summary

Strengths and limitations of this study

* A population-based cohort of adoptees with FASD, avoiding clinic-based bias.

* Face-to-face clinical evaluations by the same assessors in childhood as adulthood, with a mean follow-up time of 15.5 years

* Small sample size

* Clear separation of innate effects of alcohol exposure and effects of postnatal deprivation not possible

INTRODUCTION

The link between prenatal alcohol exposure and brain injury has been known to exist for centuries.[1] With the independent recognition of alcohol-related malformations, by Lemoine, Ulleland, Smith, Jones, and colleagues, a clinical syndrome was identified which eventually became known as Fetal Alcohol Syndrome (FAS).[2,3] Since then, major contributions in epidemiological and teratological research have corroborated the deleterious effects of alcohol exposure during pregnancy, elucidating the pathogenic mechanisms of alcohol on the face and brain in particular.[4,5] A spectrum of alcohol effects on embryonic and fetal development has been recognized, and is today known as fetal alcohol spectrum disorders (FASD). Diagnostic criteria differ somewhat between countries, but the key features of FAS – growth deficiency, facial dysmorphology, and neurobehavioral impairment – remain the same as originally described.[6] The clinical criteria for FASD, according to Hoyme et al,[5,7] recognize that individuals with all key features have FAS, whereas those with facial dysmorphology and neurobehavioral impairment are recognized as having partial FAS (PFAS), and those with confirmed alcohol exposure and neurobehavioral impairment as having alcohol-related neurodevelopmental disorder (ARND). Finally, concurrent facial dysmorphology and structural birth defects are diagnosed as alcohol-related birth defect (ARBD).

Although epidemiological studies and estimates of FASD consistently report minimum prevalence rates of 1.1-5%,[8–12] the contribution from alcohol exposure during pregnancy to the global economic and health burden is frequently overlooked[13,14] and is deemed grossly underestimated.[15]

The literature on the consequences of FASD in adulthood is limited, but there are indications of persistence of disabilities and need for long-term support.[16] However, to distinguish the

effects of prenatal alcohol exposure from those of an adverse postnatal rearing environment has been a methodological challenge, since children with FASD are at increased risk of unstable family relations and placements, orphanages, and adoptions.[17–19] The limited evidence available suggests that adoption is associated with higher levels of emotional security and general wellbeing than provided by impermanent placements, and therefore poses the best long-term alternative.[20,21]

Aims of the Study

The aim was to characterize young adult outcome of FASD in an optimized rearing environment, and to evaluate the diagnostic stability of FASD into adulthood.

MATERIAL AND METHODS

Design, Setting and Participants

In a previous population-based study we invited all children adopted to western Sweden during 1990–1995 from Russia, Poland, Romania, Latvia, or Estonia. Of 99 children invited, data on 76 children upon arrival at a mean age 2,8 years was reported.[22] After a series of thorough examinations at age 5-10 years, we found previously undiagnosed neurodevelopmental disorders in 64 of 71 children (90%)[23] and ocular abnormalities in 56 of 72 (78%).[24,25] For 37 (52%), a FASD diagnosis according to the criteria described by Hoyme et al,[7] and with ascertained alcohol exposure, was confirmed in childhood.[23] It is since then recognized that a frequent reason for leaving a child in an orphanage in this region includes maternal alcohol abuse.[26] Because of insufficient data about many parents, exposure and birth status, 52% likely reflected a minimum rate of FASD in our cohort. We thought this information bias made comparisons to those in the cohort without FASD invalid. Therefore, only the 37 individuals with diagnosed FASD were invited for follow-up visits in young adulthood (18-28 years).

Assessment at adult follow-up

Assessment consisted of up to three evaluations of the participants' social, medical, psychiatric, ophthalmological and psychological status. Half of the cohort was seen in 2014, the other half in 2017–2018.

Social evaluation

A structured questionnaire covering educational attainment and current social circumstances was used, generally administered to parents by phone, and clarified at the medical examination.

Medical evaluation

Lung and heart auscultation, neurological examination of reflexes, muscle tone, finger to nose test and heel to shin test, and diadochokinesis test were performed. Measurements of height, weight, body mass index (BMI), occipitofrontal circumference (OFC), and blood pressure (BP) were recorded and converted to appropriate standard deviations (SDs) and percentile scores. Blood pressure and heart rate were recorded according to instructions by the US National High Blood Pressure Education Program.[27] Upper lip and philtrum were assessed independently and were scored using the Lip–Philtrum Guide.[5,7] Lip and philtrum rating at the first assessment was done with a scale that preceded the one currently in use.[28] To enable comparison of diagnostic domains of FASD in childhood and at follow-up in adulthood, frontal photos of the participants taken at first assessment were rated using the Hoyme et al's Lip–Philtrum Guide (2016). Pain or sleep problems were present if a significant disturbance was reported at least once a week.

Psychiatric evaluation

To assess for affective psychotic disorders, substance abuse, and antisocial personality disorder, the Mini International Neuropsychiatric Interview 6.0.0 (MINI)[29] was used. Presence of attention deficit hyperactivity disorder (ADHD) was assessed with questions from

the Adult ADHD Self-Report scale 1.1 (ASRS).[30] Because young adults tend to underestimate ADHD symptoms,[31] the assessment was informed by family, the medical records, other measures when available, and clinical judgment. Based on all available information, the clinical condition was evaluated with the Clinical Global Impression-severity (CGI-S) instrument, using an ordinal scale where 1 = "normal" and 7 = "extremely ill."[32] The scoring rationale for the CGI-S and clinical vignettes exemplifying each score can be found in the Supplementary file.

Ophthalmological evaluation

An ophthalmological assessment of visual acuity, refraction, strabismus and structural abnormalities was made with the same procedure as in the original study.[23] An in-depth report of the ophthalmological assessment will be published elsewhere.

Psychological evaluation

Leiter-Revised (Leiter-R) non-verbal tests,[33] consisting of an intellectual quotient (IQ) test of fluid reasoning and visualization, as well as the Leiter-R Attention and Memory battery, were administered. The Leiter-R rating scales for parents and psychologists, and the Adaptive Behavior Assessment Scale (ABAS-II) parent form[34] were also administered. The testing was conducted by the same psychologist (L.S.) as in the original study.[23]

Ethics

The study was approved by the Regional Ethical Review Board, Gothenburg, and written informed consent was received from the participants.

Patient and Public involvement

Patients were not directly involved in the design, recruitment or in the conduct of this study.

Statistical methods

Version 22 of SPSS (IBM Corp., Chicago, IL, US) was used for all analyses. Frequencies, means, SDs, medians and ranges were calculated for descriptive purposes. When comparing continuous data being reassessed, paired samples test was performed. For detection of subgroup differences, Kruskal-Wallis test was used.

RESULTS

The follow-up cohort consisted of 36 of 37 individuals (97%), 15 female, with a median age of 22 years (range 18–28 years) and a median follow-up time of 15.5 years (range 13–17 years). Half of the group seen in 2014 were mainly individuals with a FAS-diagnosis. The social interview was completed by 36 individuals, the medical and psychiatric examination by 32, the ophthalmological by 30 and the psychological examination by 29. Medical charts contributed additional data for some individuals. Morbidity, reluctance towards further investigations, and the inconveniences of traveling were reasons for participation in only some of the tests.

Social evaluation

The participants' social circumstances are shown in Table I.

Table I. Social Circumstances of Adoptees with Fetal Alcohol Spectrum Disorders in Young Adulthood

	(n=36)
Highest completed education	
Special education	14 (39)
Primary school, 9 years	9 (25)
Secondary school, 12 years	11 (31)
Attempted university studies	2 (5)
Criminality	
Victim of sexual crime[a]	9 (26)
Victim of physical assault	4 (12)
Criminal convictions[b]	2 (6)
Income and compensation	
Working	11 (31)
Social welfare	10 (28)
Disability pension	10 (28)
Student	5 (14)

Values expressed as numbers and percentages.
[a]Reported by six women and three men.
[b]Two men reported convictions for drug-related theft and violence.

Medical evaluation

Measurements and traits within the diagnostic domains of FASD at the time of diagnosis and at follow-up are summarized in Figure 1. Mean SDs of weight, length, head circumference, and BMI at four measurements for the FAS group are depicted in Figure 2. Symptoms, findings, and health measures reported at the medical assessment are presented in Table II.

TABLE II. Medical Examination of Adoptees with Fetal Alcohol Spectrum Disorders in Young Adulthood

	(n=32)
Any abnormal motor finding	22 (69)
Dysdiadochokinesis	15 (47)
Balance disturbance	5 (16)
Abnormal muscle tone	4 (13)
Ataxia	2 (6)
Abducens paresis	1 (3)
Any somatic complaint	24 (75)
Sleep disturbance	15 (41)
Headache	11 (30)
Other pain	10 (27)
Stomach disturbance	6 (16)
	(n=35)[b]
Any metabolic risk factor	18 (51)
Body mass index ≥25	10 (30)
Tobacco smoker	7 (20)
Hypertensive[a]	9 (28)
Prehypertensive	3 (9)
Any psychotropic medication	16 (46)
ADHD medication	8 (23)
Antidepressants	7 (20)
Neuroleptic	3 (9)
Anticonvulsant	3 (9)
Asthma treatment	3 (9)

Values expressed as numbers and percentages.

[a]Three individuals were concurrently receiving attention deficit hyperactivity disorder (ADHD) medication.

[b]Information was obtained via telephone and from the medical records in three additional cases.

Psychiatric evaluation

Results of the psychiatric interviews are summarized in Table III.

Table III. Psychiatric Assessment of Adoptees with Fetal Alcohol Spectrum Disorders in Childhood and Young Adulthood

DSM-IV diagnosis	
Childhood[a]	(n=37)
Any disorder	30 (81)
Attention deficit hyperactivity disorder	23 (62)
Oppositional defiant disorder	16 (43)
Developmental coordination disorder	15 (41)
Tic disorder	5 (14)
Autism	2 (5)
Conduct disorder	2 (5)
Obsessive compulsive disorder	1 (3)
Adulthood[b]	(n=33)
Any disorder	29 (88)
Attention deficit hyperactivity disorder	23 (70)
Any anxiety disorder	17 (52)
Social phobia	8 (24)
Panic disorder	7 (21)
Generalized anxiety disorder	7 (21)
Agoraphobia	5 (15)
Three or more disorders[c]	16 (48)
Any depressive episode	14 (42)
Self-injurious behavior	8 (24)
Suicide attempt	7 (21)
Autism	4 (12)
Substance use disorder	4 (12)
Manic or hypomanic episode	3 (9)
Antisocial personality disorder	2 (6)
Obsessive compulsive disorder	2 (6)
Eating disorder	2 (6)
Psychotic disorder	1 (3)
CGI-S score[d]	
1 = normal	2 (6)
2–3 = borderline to mildly ill	5 (15)
4–5 = moderately to markedly ill	6 (18)
6–7 = severely to extremely ill	21 (62)

Data are presented as numbers (and percentages). CGI-S = Clinical Global Impression - Severity; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition.
[a]Childhood diagnosis was based on evaluation by a pediatrician, psychologist, and ophthalmologist.
[b]The diagnostic rationale is described under "Methods."
[c]In the composite measure of "three or more disorders," multiple anxiety disorders in the same individual are considered as one. Suicide attempt and self-injurious behavior are not included.
[d]See Appendix I S1 for the scoring rationale and clinical vignettes.

Substance use disorders were found in two cases each of polysubstance use and alcohol use. A formalized evaluation of autistic traits was not part of the assessment, but four individuals reported having been diagnosed with autism outside the study. Past and/or present contact with adult psychiatry was reported by 18 individuals (50%). Participants with FAS had higher CGI-S scores, but in post-hoc analyses no significant differences between the FASD subgroups were found (Kruskal-Wallis test; p=0.07). Clinical vignettes with CGI-S scores are found in online supplementary appendix S1.

Ophthalmological evaluation

Measurements of inner canthal distance (ICD) and palpebral fissure length (PFL) are given in online supplementary table IV, S2. In the cohort, findings of ophthalmological abnormalities, such as low visual acuity, refractive errors, strabismus, ptosis and intraocular abnormalities (increased tortuosity of retinal vessels, abnormal optic disc), were seen in 32 out of 37 (86%) in childhood,[24] and in 29 out of 30 (97%) at follow-up.

Psychological evaluation

Scores for the Leiter-R IQ and ABAS-II are shown in online supplementary table V, S3. Increased deficits in adaptive and cognitive functions in relation to the expected trajectory were noted by the psychologist. In a post-hoc analysis of the baseline median IQ score of 86, the median IQ at follow-up was significantly lower, 71 (paired samples test mean difference: 15.4; 95% confidence interval [CI] 9.5–21.4). When comparing only individuals with data at both time points (childhood and adulthood, n=29), the difference remained significant (paired samples test mean difference 18.9; 95% CI 12.7-25.0).

DISCUSSION

This observational, population-based cohort study provides insight into the long-term outcomes in young adulthood of children with FASD raised in an optimal environment. In summary, the proportion still meeting diagnostic criteria for FASD in adulthood was substantial, and participants exhibited high rates of social dependency, medical, psychiatric, ophthalmological symptoms and cognitive impairments.

Individuals with FASD has been underrecognized, and overrepresented among individuals in out-of-home placements.[18,19,35] Therefore we think the findings from this group of adoptees with FASD has external validity when applied to individuals in out-of-home placement for similar reasons, i e maternal drug abuse, and that country of origin or age at adoption, are of subordinate importance. Because alcohol exposure is rarely assessed biochemically or with adequate interview techniques,[5,36] it is often underestimated and may confound comparisons with other cohorts. Results must be interpreted with caution due to the small sample size, but can be compared to the few studies of adults prenatally exposed to alcohol, raised in chaotic family situations or in institutional care, allowing some inference about the role of optimal environment.[17,35,37]

The proportion of participants with FASD graduating from secondary school after 12 years of education (36%) in this cohort is substantially lower than that reported for earlier groups of Swedish adoptees, adopted due to national crises of war, rather than drug abuse (Of 8000 individuals adopted from Asian countries to Sweden during the 1970s, graduation was achieved in slightly lower rates (80%) compared to Swedish-born peers (85%)).[38] At an age of around 40 years, 11% of Asian adoptees were dependent predominately on social support, in comparison to 5% of the general population,[38] which is substantially lower than the 56%

reported for this younger cohort. This rate is in line with a Swedish registry-based follow-up of 72 individuals with FASD, with a 51% unemployment rate at a mean age of 32 years.[35] The differences suggest innate, rather than social, factors as determinants of social prognosis. Streissguth, studying a clinical sample of 90 young adults with FASD,[39] estimated a 60% lifetime prevalence of delinquency, which is in contrast to the prevalence of 6% found in this study. We hypothesize that the transition to a relatively stable social environment of adoption outside of big cities mitigates this risk.

When diagnostic criteria are revisited in adulthood the proportion fulfilling the anthropometric criteria are somewhat decreased. The philtrum and lip rank is still high, but this criterion must be interpreted with caution as it may suffer from observer bias, and absence of validated scales for dysmorphological evaluation of FASD in adults. This highlights the difficulty of diagnosing FASD in adulthood, and the need for complementary diagnostic methods.

The anthropometric measurements of the FAS group were below the population mean at all time points. The markedly small head circumference and stunted height, noted upon arrival in Sweden, probably represents a consequence of prenatal suboptimality in general and alcohol exposure in particular, followed by an unfavorable rearing environment.[22] The arrival to a more favorable milieu as these children were adopted resulted in a partial correction of the stunted growth patterns towards normal ranges; however, these patterns returned in adulthood when stunted growth figures of -2 SD for height and head circumference were measured. On the other hand, BMI steadily increased from arrival to adulthood and can be expected to continue with increasing age, in line with secular trends.[40] Stunted growth patterns in children when encountered clinically should not only be evaluated medically but also longitudinally, using thorough multidisciplinary neurodevelopmental examinations.[41]

High BP was found in nine (28%) individuals. Unfortunately, repeat measurements were not possible. The expected prevalence of hypertension at this age in this setting is 2%.[42] In conjunction with elevated rates of smoking and increasing BMI, the high rate in our cohort may signal an impending health concern. The Barker hypothesis states that ailments of adulthood, such as cardiovascular disease and metabolic syndrome, have fetal origins.[43] Studies of preterm birth and low birth weight support this hypothesis.[44] Alcohol exposure, being related to both preterm birth and low birth weight, may therefore be an underestimated factor for fetal origins of disease, and warrants further longitudinal study.[45]

The lifetime prevalence of epilepsy increased from one (3%) in childhood to three (8%) in young adulthood. Epilepsy was added to the 2016 revised criteria for FASD.[5] Incidence of epilepsy is known to have a second peak in adolescence,[46] and additional studies on adults may increase estimates of lifetime prevalence of epilepsy in FASD.

Motor abnormalities were found at similar rates in adulthood (69%) as in childhood (68%). This is in line with a study by Connor et al, where coordination problems persisted into adulthood for a clinical sample of 60 individuals with FASD.[47] A few studies indicate persisting dysdiadochokinesis predictive of psychiatric morbidity in adulthood, such as schizophrenia and anorexia nervosa.[48,49] The findings agree with the literature on soft motor signs being overrepresented among individuals with psychiatric morbidity, of whom individuals with FASD may constitute a substantial minority, given that 50% already reported contact with adult psychiatry. A relation between alcohol exposure and decreased basal ganglia volume has been described.[50] Basal ganglia have been implicated in developmental coordination disorder (DCD) and learning disabilities, as well as ADHD.[51] Despite early reports of DCD in FAS,[52] domains of coordination are not incorporated into diagnostic criteria. The persisting motor impairments and associated cognitive deficits caused by

prenatally acquired brain injury that constitutes FASD, suggest that FASD could be included under the umbrella term of cerebral palsy.[53]

The proportion exhibiting small palpebral fissures had decreased considerably by adulthood (76% vs 47%). Asymmetry, as captured by a difference in ICD and PFL ≥5 mm, was likewise somewhat decreased (46% vs 35%). Clinical presentations with asymmetrical growth pattern can raise concerns about FASD in addition to other genetic syndromes.[54] Although the correlation between OFC and PFL has been assumed to be strong,[55] the variance in PFL, explained by OFC where studied, is at best 15%.[56] Whereas brain growth drives the growth of the head, PFL is better understood as related to factors other than crude brain size, such as growth of the eye[56] and the forebrain.[57] The correlation between ICD and PFL in patients with FASD has been weak,[55] and ICD may therefore capture aspects of neurodevelopment not captured by PFL.

Nonspecific somatic complaints have previously been reported in association with, and preceding, affective disorders,[58] both of which were common in this cohort. The heritability of affective disorders has been estimated to be 40%.[59] Given that alcohol abuse sometimes indicates self-medication,[60] a genetic liability may be overrepresented in FASD independently of the alcohol exposure itself. In addition, traumatic experiences in childhood, academic and professional failure, and underachievement relative to peers pose an environmental substrate for demoralization and chronic stress, increasing liability for affective disorders.[59]

The rates of depression, anxiety disorders and suicide attempts found in this cohort correspond to findings of earlier studies.[37,39,61] Executive dysfunction and marked attention problems have been highlighted elsewhere[17,37] but this is, to our knowledge, the first study in adults with FASD assessing criteria for ADHD. The increase in ADHD from childhood (62%) to adulthood (70%) may reflect both parents' tolerance for executive

dysfunction in childhood and increased demands on executive function in adulthood. However, lower symptoms of impulsivity and less deviant social interactions in adulthood, based on standardized testing, could lead researchers to overestimate the functioning of adults with FASD, a point reiterated by researchers in the field of FASD.[17,62]

In this cohort, psychotic disorders were rare (3%), which is in contrast to results by Famy et al,[63] who report mainly brief psychotic disorder, in 40% of 25 studied individuals with FASD. The relation between psychotic disorders and substance dependence in that sample is not discussed. The rate of depression (44% vs 42%) and psychiatric disorders in general (92% vs 88%) was similar.

Mukherjee et al[64] compared children with FASD exposed (n=45) and not exposed (n=52) to prolonged neglect, and found no significant difference in neurodevelopmental morbidity. They concluded from their sample that alcohol exposure and innate factors explain neurodevelopmental morbidity alone, independently of neglect. This is in line with a recent twin study, where monozygotic twins, despite being differentially exposed to childhood maltreatment, were concordant regarding symptom rates of neurodevelopmental disorders.[65] In a longitudinal study of English and Romanian adoptees, by Sonuga-Barke et al, two cohorts who spent >6 months vs <6 months in an institution were compared. Rates of emotional distress (45% vs 18%) and ADHD symptoms (32% vs 12%) were higher in the group with prolonged institutionalization.[66] Despite higher rates of extremely low birth weight <2500 g (32.9% vs 22%) in the group with the prolonged stay, and limited reports of perinatal risks such as gestational age, alcohol exposure, birth head circumference, or any dysmorphology assessment during the study, the difference in neurodevelopmental outcome was attributed mainly to institutional deprivation. It is worth noting that 30% of the initial cohort in our study were adoptees from Romania, born in the same years as the participants in Sonuga-Barke et al's cohort',[22] but generally adopted at a later age (mean age 3.3 years).

Given the high minimum rate of confirmed alcohol exposure in our initial sample (52%), and the fact that institutions prioritize healthier children for internal adoptions at a young age, a bias towards higher rates of alcohol exposure may be a substantial source of confounding in their group of adoptees.[66]

A review by Kable et al summarizes the literature on neurobehavioral deficits in FASD, specifically deficits in neurocognition, self-regulation, and adaptive behavior.[62] A characteristic of FASD is increasing adaptive deficits with age, relative to peers. A higher than expected rate of autism has been reported previously in FASD,[67,68] and deficits in social skills and communication are part of the adaptive deficits described. Adult adaptive functioning requires goal-directed behavior, abstract thinking, generalization of cause and effect, managing household, finances, and social relations – all functions that are inseparable from neurocognition and self-regulation. The decrease in non-verbal IQ to adulthood indicates that stunted growth in FASD applies not only to weight and length, but also to brain maturation and function, and corresponds to the adaptive deficits. To our knowledge, this marked decrease in IQ has not previously been demonstrated in the literature on FASD. The non-verbal tests cover spatial reasoning, working memory, problem solving, logical reasoning, and generalization, higher order functions requiring efficient interconnectivity of large brain areas.[69] An underlying deficit in these higher order brain functions would be expected to affect proficiency in complex tasks in general, not just one, becoming more evident with age.

Conclusions

Children with FASD have a prenatal brain injury, often associated with compounding effects from postnatal deprivation and unstable social circumstances. These children require rehabilitation, special education and social support. This is accomplished by assessment and

care by pediatricians, psychologists, allied health professionals, and teachers, beginning in childhood and across the lifespan.

Figure 1. Diagnostic domains of fetal alcohol spectrum disorders in childhood and young adulthood in 37 adoptees

Figure 2. Anthropometric measurements at four time points for 21 adoptees with fetal alcohol syndrome

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Author contributions: Magnus Landgren, Marita Andersson Grönlund. Leif Svensson, and Eva Aring conceptualized the study, collected data, and reviewed the manuscript for important intellectual content.

Emelie Gyllencreutz collected data, carried out initial analyses, and reviewed the manuscript for important intellectual content.

Valdemar Landgren collected data, carried out initial analyses, and drafted the initial manuscript.

All authors have approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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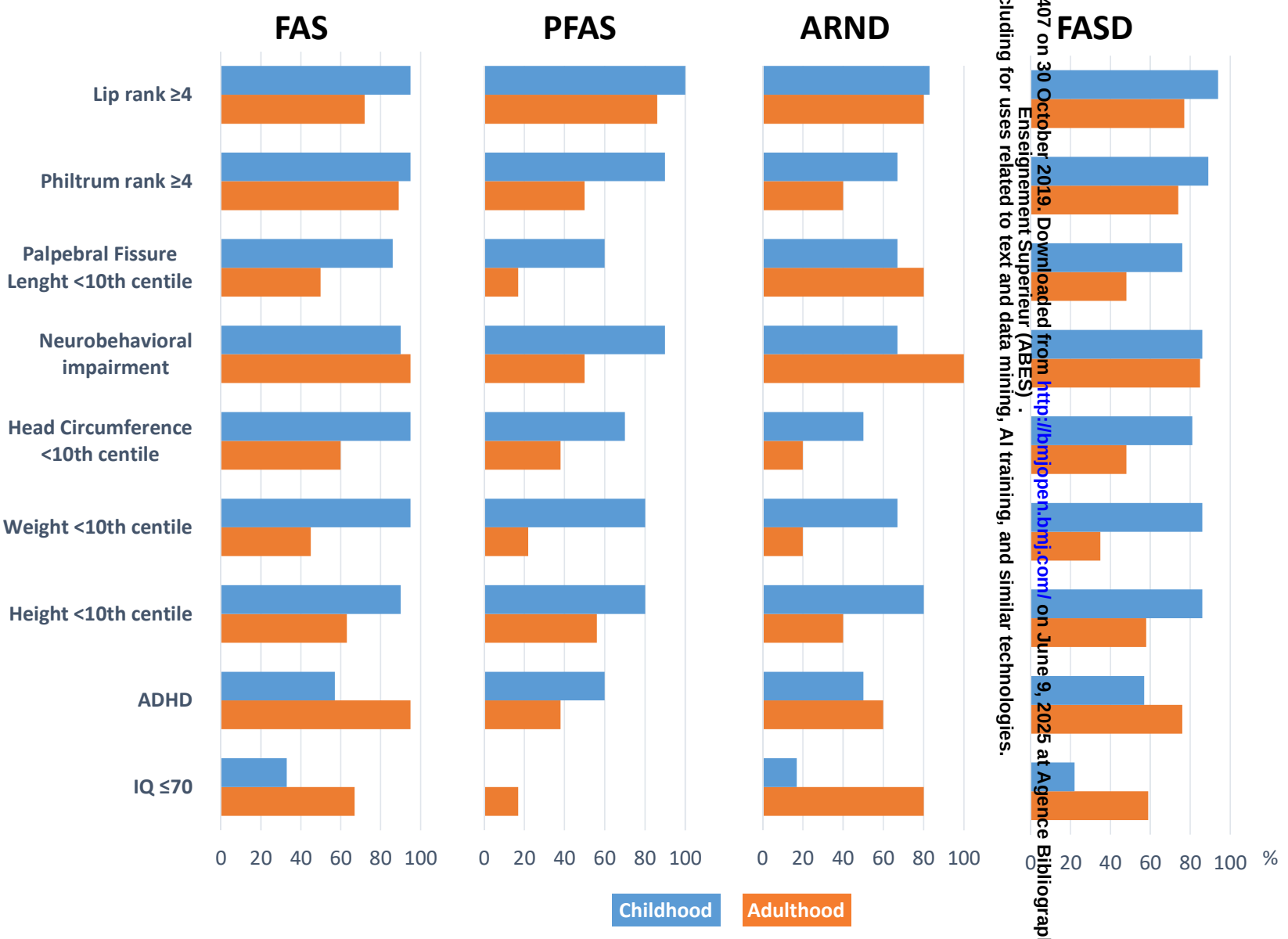

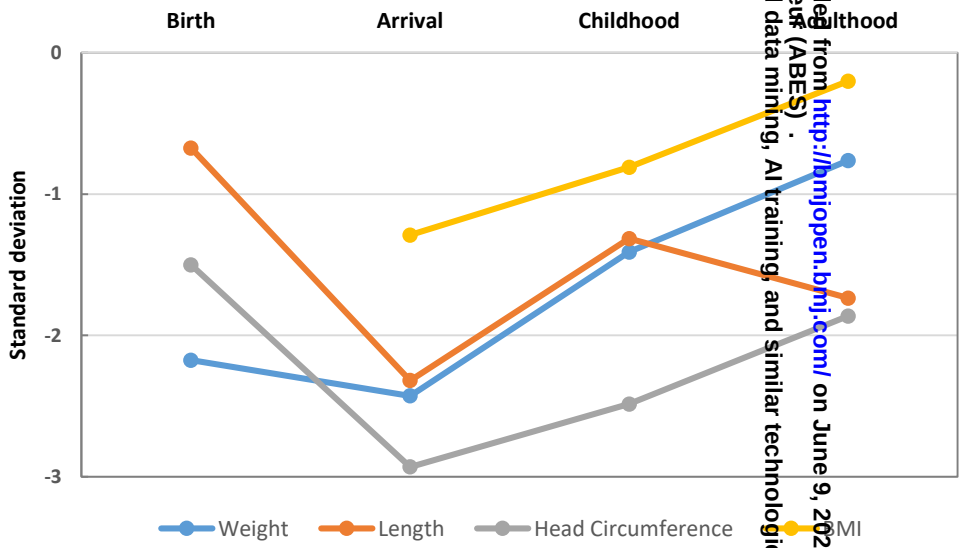

Supplementary Appendix S1 – Clinical Vignettes

The CGI-S was developed to capture clinical impressions of patients participating in clinical trials of psychiatric disorders that transcend mere symptom checklists. It has been utilized together with the impression of improvement (CGI-I) scores from the therapy under study. The CGI-S measures overall function and symptom severity on an ordinal scale from 1 to 7. The scoring rationale of the CGI-S may differ between diseases and trials. For the purpose of this study, the scoring was adapted from the guidelines of Busner et al, where 1 = "normal," 2 = "borderline mentally ill," 3 = "mildly ill" (with minimal impairment), 4 = "moderately ill" (warrants medication), 5 = "markedly ill" (has significantly impaired occupational function), 6 = "severely ill" (requires assistance from others), and 7 = "extremely ill" (may be hospitalized). Clinical vignettes for each score are presented below. In the vignettes, some identifying details have been changed to protect the privacy of individuals.

CGI 1 – Normal:

A woman with ADHD and PFAS at index evaluation completed 12 years of school and 2 years of post-secondary qualified education. She has a history of suicide attempt as a teenager, but exhibits no psychopathology upon evaluation. She medicates for generalized epilepsy. Her current IQ is 102, and her ABAS-II score 114. She lives with a partner and holds a regular job.

CGI 2 – Borderline mentally ill:

A woman with ADHD, DCD, oppositional defiant disorder (ODD), and ARND at index evaluation completed 12 years of school and 2 years of qualified vocational education. She has a history of suicide attempt as a child, and exhibits symptoms of hyperactivity, but no present ADHD or other psychopathology upon evaluation. Her current IQ is 63, andher ABAS-II score 116. She lives independently and holds a regular job.

CGI 3 – Mildly ill:

A man with microcephaly, ADHD, DCD, ODD, and FAS at index examination who completed 12 years of regular school. He reports a history of depression and screens positive for agoraphobia, post-traumatic stress disorder (PTSD), and persistent ADHD. His IQ is 62, his ABAS-II score 92. He lives with her parents and attends an adult education college.

CGI 4 – Moderately ill:

A woman with DCD, ODD, and ARND at index examination attended school for 12 years. She is studying to get her school grades as mental health issues in her teenage years had prevented her from obtaining them while at school. She reports a history of depression, screens positive for ADHD (inattentive type), and medicates with antidepressants. Her IQ is 62 andher ABAS-II score 64. She has not held a job, and lives with her sibling.

CGI 5 – Markedly ill:

A woman with partial cognitive dysfunction, DCD, and ARND at index. She has completed 12 years of schooling at a school for intellectually disabled children. She exhibits no psychopathology upon evaluation and has no medication. Her IQ is 58, and her ABAS-II score 114. She lives with a partner and has a son. She has regular contact with his adoptive parents, receives assistance for management of personal finances, and holds a government-supported internship at a store.

CGI 6 – Severely ill:

A man with mild intellectual disability, ADHD, and FAS at index examination who has received education for the intellectually disabled. He has persistent ADHD, screens positive for bulimia and PTSD, reports a history of depression, self-harm, suicide attempt, and rape, and has several pain problems. His IQ is 56, andhis ABAS-II score 48. He has no medication, lives alternately in supportive housing and with his adoptive parents, and receives permanent financial support.

CGI 7 – Extremely ill:

A woman with mild intellectual disability, epilepsy, ADHD, and FAS at index examination who has received education for the intellectually disabled. She has persistent ADHD and medicates for epilepsy and behavioral dysfunction. Her IQ is 36, and her ABAS-II score 46. She lives in a group home and receives permanent financial support.

Supplementary Table IV S2. Ophthalmological Assessments in Adoptees with Fetal Alcohol Spectrum Disorders in Childhood and Young Adulthood

	Childhood (n=37)	Adulthood (n=29)[a]
Palpebral fissure length		
Right eye, median, mm (range)	25 (21–29)	29 (24–32)
Left eye, median, mm (range)	25 (21–29)	29 (24–32)
Mean z-score (SD)	-1.6 (0.9)	-1.4 (1.7)
Inner canthal distance		
Median, mm (range)	29 (24–35)	32 (26–37)
Mean z-score (SD)	-0.2 (1.2)	0.0 (1.2)
ICD≥5–10 mm>PFL[b], n (%)	17 (46)	10 (35)

Z-scores are calculated according to Hall et al.[29]

[a]Of 30 examined, outer ocular measurements were missing in one case.

[b]ICD≥5–10mm>PFL is defined as a difference of ≥5 mm between the inner canthal distance (ICD) and the length of the smallest palpebral fissure (PFL) in the same individual.

Supplementary Table V S3. Psychological Assessments of Adoptees with Fetal Alcohol Spectrum Disorders in Childhood and Young Adulthood

Intellectual Quotient		n
Childhood	86 (50–107)	37
Adulthood	71 (36–121)	29
>85	3 (10)	
70-85	7 (24)	
<70	19 (66)	
Leiter-R scores regarding cognitive and social abilities rated by the psychologist		
Childhood	85 (66–106)	37
Adulthood	89 (81–110)	29
>85[a]	24 (83)	
<85[b]	5 (17)	
Adaptive behavior assessment scores in adulthood rated by parents		26
Cognitive function	65 (40–114)	
Social function	65 (50–112)	
Practical function	78 (58–120)	
General abilities	66 (40–120)	

Data is presented as median (range) or numbers (percentage) as appropriate.

[a]One out of five was on ADHD medication.

[b]Six out of 24 were on ADHD medication.

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3

Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of	6-8

		assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	9
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	9
Statistical methods	#12c	Explain how missing data were addressed	N/A because statistical analyses and comparisons were not part of aims
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	N/A
Statistical methods	#12e	Describe any sensitivity analyses	N/A

Results

Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	6, 9
Participants	#13b	Give reasons for non-participation at each stage	9
Participants	#13c	Consider use of a flow diagram	Text on page 6 and 9
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	tables
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	tables
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	9
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	N/A
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision	N/A

		(eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	N/A
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	15
Discussion			
Key results	#18	Summarise key results with reference to study objectives	16
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	16
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	16-22
Generalisability	#21	Discuss the generalisability (external validity) of the study results	16
Other			

Information

Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

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Fetal Alcohol Spectrum Disorders from Childhood to Adulthood: A Swedish Population Based Naturalistic Cohort Study of Adoptees from Eastern Europe

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Fetal Alcohol Spectrum Disorders from Childhood to Adulthood: A Swedish Population Based Naturalistic Cohort Study of Adoptees from Eastern Europe

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Short title: Fetal alcohol spectrum disorders from child to adult

Keywords: Fetal Alcohol Syndrome, Attention Deficit Disorder with Hyperactivity, Motor Skills Disorders, Mental Retardation, Adoption

Abbreviations:

ABAS-II = Adaptive Behavior Assessment Scale II

ADHD = Attention Deficit Hyperactivity Disorder

ARBD = Alcohol-Related Birth Defect

ARND = Alcohol-Related Neurodevelopmental Disorder

BMI = Body Mass Index

BP = Blood Pressure

CGI-S = Clinical Global Impression-Severity scale

DCD = Developmental Coordination Disorder

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition

ICD = Inner Canthal Distance

IQ = Intelligence Quotient

MINI = Mini International Neuropsychiatric Interview 6.0.0

OFC = Occipitofrontal Circumference

PFAS = Partial Fetal Alcohol Syndrome

PFL = Palpebral Fissure Length

Word count: 3405 words.

Abstract

Background

Fetal Alcohol Spectrum Disorders (FASD) are a global health concern. To further understand FASD in adulthood is a major public health interest.

Objective

To describe the clinical characteristics of young adults with FASD adopted from orphanages to a socially more favorable and stable rearing environment as children.

Design

Prospective observational cohort study

Setting

Western Sweden

Participants

A population-based cohort of thirty-seven adoptees diagnosed with FASD in childhood.

Outcome measures

Assessment consisted of clinical evaluations of social, medical, psychiatric, neuropsychological, adaptive, and ophthalmological status by a physician, ophthalmologist, orthoptist, and psychologist.

Results

Out of 37 adoptees with FASD, 36 (15 females) were evaluated at a median age of 22 (range 18–28) years and a mean follow-up time of 15.5 years (range 13-17). Twenty (56%) were dependent on social support. Sexual victimization was reported by nine (26%). In 21 individuals with fetal alcohol syndrome, growth restriction in height and head circumference of approximately -1.8 standard deviations persisted into adulthood. Of 32 examined, 22 (69%) had gross motor coordination abnormalities. High blood pressure was measured in nine (28%). Ophthalmological abnormalities were found in 29 of 30 (97%). A median IQ of 86 in childhood had declined significantly to 71 by adulthood (mean difference: 15.5; 95% confidence interval 9.5–21.4). Psychiatric disorders were diagnosed in 88%, most commonly attention deficit hyperactivity disorder (70%). Three or more disorders were diagnosed in 48%, and 22% had attempted suicide. The median Clinical Global Impression-Severity score was 6 = “severely ill.”

Conclusion

Major cognitive impairments, psychiatric morbidity, facial dysmorphology, growth restriction and ophthalmological abnormalities accompanies FASD in adulthood. Recognition of FASD in childhood warrants habilitation across the lifespan.

Article Summary

Strengths and limitations of this study

- A population-based cohort of adoptees with FASD, avoiding clinic-based bias.
- Face-to-face clinical evaluations by the same assessors in childhood as adulthood
- Small sample size decreases the precision of results and their generalizability
- No particular comparison group of adoptees without FASD.
- A clear separation of innate effects of alcohol exposure and postnatal deprivation not possible, although adoption infers an optimization of the environment compared to orphanage.

INTRODUCTION

The link between prenatal alcohol exposure and brain injury has been known to exist for centuries.[1] With the independent recognition of alcohol-related malformations, by Lemoine, Ulleland, Smith, Jones, and colleagues, a clinical syndrome was identified which eventually became known as Fetal Alcohol Syndrome (FAS).[2,3] Since then, major contributions in epidemiological and teratological research have corroborated the deleterious effects of alcohol exposure during pregnancy, elucidating the pathogenic mechanisms of alcohol on the face and brain in particular.[4,5] A spectrum of alcohol effects on embryonic and fetal development has been recognized, and is today known as fetal alcohol spectrum disorders (FASD). Diagnostic criteria differ somewhat between countries, but the key features of FAS – growth deficiency, facial dysmorphology, and neurobehavioral impairment – remain the same as originally described.[6] The clinical criteria for FASD, according to Hoyme et al,[5,7] recognize that individuals with all key features have FAS, whereas those with facial dysmorphology and neurobehavioral impairment are recognized as having partial FAS (PFAS), and those with confirmed alcohol exposure and neurobehavioral impairment as having alcohol-related neurodevelopmental disorder (ARND). Finally, concurrent facial dysmorphology and structural birth defects are diagnosed as alcohol-related birth defect (ARBD).

Although epidemiological studies and estimates of FASD consistently report minimum prevalence rates of 1.1-5%,[8–12] the contribution from alcohol exposure during pregnancy to the global economic and health burden is frequently overlooked[13,14] and is deemed grossly underestimated.[15]

The literature on the consequences of FASD in adulthood is limited, but there are indications of persistence of disabilities and need for long-term support.[16] However, to distinguish the

effects of prenatal alcohol exposure from those of an adverse postnatal rearing environment has been a methodological challenge, since children with FASD are at increased risk of unstable family relations and placements, orphanages, and adoptions.[17–19] For children separated from their family, evidence suggests that adoption is associated with higher levels of emotional security and general wellbeing than provided by impermanent placements or orphanages, and therefore poses the best long-term alternative.[20,21]

Aims of the Study

The aim was to characterize young adult outcome of FASD in a socially favorable rearing environment, and to evaluate the diagnostic stability of FASD into adulthood.

MATERIAL AND METHODS

Design, Setting and Participants

In a previous population-based study all children adopted to western Sweden during 1990–1995 from Russia, Poland, Romania, Latvia, or Estonia were invited for in-depth health examinations. Of 99 children invited, data on 76 children upon arrival at a mean age 2.8 years was reported.[22] At age 5-10 years, we diagnosed neurodevelopmental disorders in 64 of 71 children (90%)[23] and ocular abnormalities in 56 of 72 (78%).[24,25] For 37 (52%), a FASD diagnosis according to the criteria described by Hoyme et al,[7] with ascertained alcohol exposure, was confirmed in childhood.[23] It has since been recognized that a frequent reason for leaving a child in an orphanage in this region includes maternal alcohol abuse.[26] Because of insufficient data about many parents, exposure and birth status, 52% likely reflected a minimum rate of FASD in our cohort. We thought this information bias made comparisons to those in the cohort without FASD invalid. Therefore, only the 37 individuals with diagnosed FASD were invited for follow-up visits in young adulthood (18-28 years).

Assessment at adult follow-up

Assessment consisted of evaluations of the participants' social, medical, psychiatric, ophthalmological and psychological status by a pediatric neurologist or resident physician, ophthalmologist, orthoptist and psychologist on up to three occasions. Half of the cohort was seen in 2014, the other half in 2017–2018.

Social evaluation

A structured questionnaire covering educational attainment and current social circumstances was used, generally administered to parents by phone, and clarified at the medical examination.

Medical evaluation

Lung and heart auscultation, neurological examination of reflexes, muscle tone, finger to nose test and heel to shin test, and diadochokinesis test were performed by the examining physician. Measurements of height, weight, body mass index (BMI), occipitofrontal circumference (OFC), and blood pressure (BP) were recorded and converted to appropriate standard deviations (SDs) and percentile scores. Blood pressure and heart rate were recorded according to instructions by the US National High Blood Pressure Education Program.[27] Upper lip and philtrum were assessed independently and were scored using the Lip–Philtrum Guide.[5,7] Lip and philtrum rating at the first assessment was done with a scale that preceded the one currently in use.[28] To enable comparison of diagnostic domains of FASD in childhood and at follow-up in adulthood, frontal photos of the participants taken at first assessment were rated using the Hoyme et al's Lip–Philtrum Guide (2016). Pain or sleep problems were present if a significant disturbance was reported at least once a week.

Psychiatric evaluation

To assess for affective psychotic disorders, substance abuse, and antisocial personality disorder, the Mini International Neuropsychiatric Interview 6.0.0 (MINI)[29] was used by the

examining physician. Presence of attention deficit hyperactivity disorder (ADHD) was assessed with questions from the Adult ADHD Self-Report scale 1.1 (ASRS).[30] Because young adults tend to underestimate ADHD symptoms,[31] the assessment was informed by family, the medical records, other measures when available, and clinical judgment. Based on all available information, the clinical condition was evaluated with the Clinical Global Impression-severity (CGI-S) instrument, using an ordinal scale where 1 = "normal" and 7 = "extremely ill."[32] The scoring rationale for the CGI-S and clinical vignettes exemplifying each score can be found in the Supplementary file.

Ophthalmological evaluation

An ophthalmological assessment of visual acuity, refraction, strabismus and structural abnormalities was made by ophthalmologist and orthoptist, with the same procedure as in the original study.[23] An in-depth report of the ophthalmological assessment will be published elsewhere.

Psychological evaluation

Leiter-Revised (Leiter-R) non-verbal tests,[33] consisting of an intellectual quotient (IQ) test of fluid reasoning and visualization, as well as the Leiter-R Attention and Memory battery, were administered. The Leiter-R rating scales for parents and psychologists, and the Adaptive Behavior Assessment Scale (ABAS-II) parent form[34] were also administered. The testing was conducted by the same psychologist (L.S.) as in the original study.[23]

Ethics

The study was approved by the Regional Ethical Review Board, Gothenburg, and written informed consent was received from the participants.

Patient and Public involvement

Patients were not directly involved in the design, recruitment or in the conduct of this study.

Statistical methods

Version 22 of SPSS (IBM Corp., Chicago, IL, US) was used for all analyses. Frequencies, means, SDs, medians and ranges were calculated for descriptive purposes. When comparing continuous data being reassessed, paired samples test was performed. For detection of subgroup differences, Kruskal-Wallis test was used.

RESULTS

The follow-up cohort consisted of 36 of 37 individuals (97%), 15 females, with a median age of 22 years (range 18–28 years) and a median follow-up time of 15.5 years (range 13–17 years). Half of the group seen in 2014 were mainly individuals with a FAS-diagnosis. The social interview was completed by 36 individuals, the medical and psychiatric examination by 32, the ophthalmological by 30 and the psychological examination by 29. Medical charts contributed additional data for some individuals. Morbidity, reluctance towards further investigations, and the inconveniences of traveling were reasons for participation in only some of the tests.

Social evaluation

The participants' social circumstances are shown in Table I.

Table I. Social Circumstances of Adoptees with Fetal Alcohol Spectrum Disorders in Young Adulthood

	(n=36)
Highest completed education	
Special education	14 (39)
Primary school, 9 years	9 (25)
Secondary school, 12 years	11 (31)
Attempted university studies	2 (5)
Criminality	
Victim of sexual crime[a]	9 (26)
Victim of physical assault	4 (12)
Criminal convictions[b]	2 (6)
Income and compensation	
Working	11 (31)
Social welfare	10 (28)
Disability pension	10 (28)
Student	5 (14)

Values expressed as numbers and percentages.
[a]Reported by six women and three men.
[b]Two men reported convictions for drug-related theft and violence.

Medical evaluation

Measurements and traits within the diagnostic domains of FASD at the time of diagnosis and at follow-up are summarized in Figure 1. Mean SDs of weight, length, head circumference, and BMI at four measurements for the FAS group are depicted in Figure 2. Symptoms, findings, and health measures reported at the medical assessment are presented in Table II.

TABLE II. Medical Examination of Adoptees with Fetal Alcohol Spectrum Disorders in Young Adulthood

	(n=32)
Any abnormal motor finding	22 (69)
Dysdiadochokinesis	15 (47)
Balance disturbance	5 (16)
Abnormal muscle tone	4 (13)
Ataxia	2 (6)
Abducens paresis	1 (3)
Any somatic complaint	24 (75)
Sleep disturbance	15 (41)
Headache	11 (30)
Other pain	10 (27)
Stomach disturbance	6 (16)
	(n=35)[b]
Any metabolic risk factor	18 (51)
Body mass index ≥25	10 (30)
Tobacco smoker	7 (20)
Hypertensive[a]	9 (28)
Prehypertensive	3 (9)
Any psychotropic medication	16 (46)
ADHD medication	8 (23)
Antidepressants	7 (20)
Neuroleptic	3 (9)
Anticonvulsant	3 (9)
Asthma treatment	3 (9)

Values expressed as numbers and percentages.

[a]Three individuals were concurrently receiving attention deficit hyperactivity disorder (ADHD) medication.

[b]Information was obtained via telephone and from the medical records in three additional cases.

Psychiatric evaluation

Results of the psychiatric interviews are summarized in Table III.

Table III. Psychiatric Assessment of Adoptees with Fetal Alcohol Spectrum Disorders in Childhood and Young Adulthood

DSM-IV diagnosis	
Childhood[a]	(n=37)
Any disorder	30 (81)
Attention deficit hyperactivity disorder	23 (62)
Oppositional defiant disorder	16 (43)
Developmental coordination disorder	15 (41)
Tic disorder	5 (14)
Autism	2 (5)
Conduct disorder	2 (5)
Obsessive compulsive disorder	1 (3)
Adulthood[b]	(n=33)
Any disorder	29 (88)
Attention deficit hyperactivity disorder	23 (70)
Any anxiety disorder	17 (52)
Social phobia	8 (24)
Panic disorder	7 (21)
Generalized anxiety disorder	7 (21)
Agoraphobia	5 (15)
Three or more disorders[c]	16 (48)
Any depressive episode	14 (42)
Self-injurious behavior	8 (24)
Suicide attempt	7 (21)
Autism	4 (12)
Substance use disorder	4 (12)
Manic or hypomanic episode	3 (9)
Antisocial personality disorder	2 (6)
Obsessive compulsive disorder	2 (6)
Eating disorder	2 (6)
Psychotic disorder	1 (3)
CGI-S score[d]	
1 = normal	2 (6)
2–3 = borderline to mildly ill	5 (15)
4–5 = moderately to markedly ill	6 (18)
6–7 = severely to extremely ill	21 (62)

Data are presented as numbers (and percentages). CGI-S = Clinical Global Impression - Severity; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition.
[a]Childhood diagnosis was based on evaluation by a pediatrician, psychologist, and ophthalmologist.
[b]The diagnostic rationale is described under "Methods."
[c]In the composite measure of "three or more disorders," multiple anxiety disorders in the same individual are considered as one. Suicide attempt and self-injurious behavior are not included.
[d]See Appendix I S1 for the scoring rationale and clinical vignettes.

Substance use disorders were found in two cases each of polysubstance use and alcohol use. A formalized evaluation of autistic traits was not part of the assessment, but four individuals reported having been diagnosed with autism outside the study. Past and/or present contact with adult psychiatry was reported by 18 individuals (50%). Participants with FAS had higher CGI-S scores, but in post-hoc analyses no significant differences between the FASD subgroups were found (Kruskal-Wallis test; p=0.07). Clinical vignettes with CGI-S scores are found in online supplementary appendix S1.

Ophthalmological evaluation

Measurements of inner canthal distance (ICD) and palpebral fissure length (PFL) are given in online supplementary table I, S2. In the cohort, findings of ophthalmological abnormalities, such as low visual acuity, refractive errors, strabismus, ptosis and intraocular abnormalities (increased tortuosity of retinal vessels, abnormal optic disc), were seen in 32 out of 37 (86%) in childhood,[24] and in 29 out of 30 (97%) at follow-up.

Psychological evaluation

Scores for the Leiter-R IQ and ABAS-II are shown in online supplementary table II, S3. Increased deficits in adaptive and cognitive functions in relation to the expected trajectory were noted by the psychologist. In a post-hoc analysis of the baseline median IQ score of 86, the median IQ at follow-up was significantly lower, 71 (paired samples test mean difference: 15.4; 95% confidence interval [CI] 9.5–21.4). When comparing only individuals with data at both time points (childhood and adulthood, n=29), the difference remained significant (paired samples test mean difference 18.9; 95% CI 12.7-25.0).

DISCUSSION

This observational, population-based cohort study provides insight into the long-term outcomes in young adulthood of children with FASD raised in a socially favorable environment. In summary, the proportion still meeting diagnostic criteria for FASD in adulthood was substantial, and participants exhibited high rates of social dependency, medical, psychiatric, ophthalmological symptoms and cognitive impairments.

Results must be interpreted with caution due to limitations. Sample size is small, and there was no specific comparison group from study initiation. Two time points for follow-up introduced a systematic bias of younger age in those with FAS, although all were 18 years or older. Educational attainment and health trajectory compared to that of older participants is therefore uncertain, and in all participants follow-up time is limited to young adulthood. However, results may be juxtaposed to the few studies of adults prenatally exposed to alcohol, raised in chaotic family situations or in institutional care. This allows for some inference about the role of environment.[17,35,36] Individuals with FASD has been underrecognized, and overrepresented among children in out-of-home placements.[18,19,36] Therefore we think the findings from this study has external validity when applied to individuals in out-of-home placement for similar reasons, i.e. maternal drug abuse, and that country of origin or age at adoption, are of subordinate importance. Because alcohol exposure is rarely assessed biochemically or with adequate interview techniques,[5,37] it is often underestimated and may confound comparisons with other cohorts.

The proportion of participants with FASD graduating from secondary school after 12 years of education (36%) in this cohort is substantially lower than that reported for earlier groups of Swedish adoptees, adopted due to national crises of war, rather than drug abuse (Of 8000

individuals adopted from Asian countries to Sweden during the 1970s, graduation was achieved in slightly lower rates (80%) compared to Swedish-born peers (85%)).[38] At an age of around 40 years, 11% of Asian adoptees were dependent predominately on social support, in comparison to 5% of the general population,[38] which is substantially lower than the 56% reported for this younger cohort. This rate is in line with a Swedish registry-based follow-up of 72 individuals with FASD, with a 51% unemployment rate at a mean age of 32 years.[36] The differences suggest innate, rather than social, factors as determinants of social prognosis. Streissguth, studying a clinical sample of 90 young adults with FASD,[39] estimated a 60% lifetime prevalence of delinquency, which is in contrast to the prevalence of 6% found in this study. We hypothesize that the transition to a relatively stable social environment of adoption outside of big cities mitigates this risk.

When diagnostic criteria are revisited in adulthood the proportion fulfilling the anthropometric criteria are somewhat decreased. The philtrum and lip rank is still high, but this criterion must be interpreted with caution as it may suffer from observer bias, and absence of validated scales for dysmorphological evaluation of FASD in adults. This highlights the difficulty of diagnosing FASD in adulthood, and the need for complementary diagnostic methods.

The anthropometric measurements of the FAS group were below the population mean at all time points. The markedly small head circumference and stunted height, noted upon arrival in Sweden, probably represents a consequence of prenatal suboptimality in general and alcohol exposure in particular, followed by an unfavorable rearing environment.[22] The arrival to a more favorable milieu as these children were adopted resulted in a partial correction of the stunted growth patterns towards normal ranges. BMI steadily increased from arrival to adulthood and can be expected to continue with increasing age, in line with secular trends.[40] However, the patterns of stunted growth figures of -2 SD for height and head

circumference returned in adulthood, and implies an altered trajectory of growth in FAS. Stunted growth patterns in children when encountered clinically should not be evaluated only medically in a strict sense, but also using thorough multidisciplinary neurodevelopmental examinations longitudinally.[41] A fragmented health care where so termed psychiatric, social or medical symptoms are assessed as isolated phenomena, otherwise struggles to detect intricate biopsychosocial patterns as exemplified by FASD.

High BP was found in nine (28%) individuals. Unfortunately, repeat measurements were not possible. The expected prevalence of hypertension at this age in this setting is 2%.[42] In conjunction with elevated rates of smoking and increasing BMI, the high rate in our cohort may signal an impending health concern. The Barker hypothesis states that ailments of adulthood, such as cardiovascular disease and metabolic syndrome, have fetal origins.[43] Studies of preterm birth and low birth weight support this hypothesis.[44] Alcohol exposure, being related to both preterm birth and low birth weight, may therefore be an underestimated factor for fetal origins of disease, and warrants further longitudinal study.[45]

The lifetime prevalence of epilepsy increased from one (3%) in childhood to three (8%) in young adulthood. Epilepsy was added to the 2016 revised criteria for FASD.[5] Incidence of epilepsy is known to have a second peak in adolescence,[46] and additional studies on adults may increase estimates of lifetime prevalence of epilepsy in FASD.

Motor abnormalities were found at similar rates in adulthood (69%) as in childhood (68%). This is in line with a study by Connor et al, where coordination problems persisted into adulthood for a clinical sample of 60 individuals with FASD.[47] A few studies indicate persisting dysdiadochokinesis predictive of psychiatric morbidity in adulthood, such as schizophrenia and anorexia nervosa.[48,49] The findings agree with the literature on soft motor signs being overrepresented among individuals with psychiatric morbidity, of whom individuals with FASD may constitute a substantial minority, given that 50% already reported

contact with adult psychiatry. A relation between alcohol exposure and decreased basal ganglia volume has been described.[50] Basal ganglia have been implicated in developmental coordination disorder (DCD) and learning disabilities, as well as ADHD.[51] Despite early reports of DCD in FAS,[52] domains of coordination are not incorporated into diagnostic criteria. The persisting motor impairments and associated cognitive deficits caused by prenatally acquired brain injury that constitutes FASD, suggest that FASD could be included under the umbrella term of cerebral palsy.[53]

The proportion exhibiting small palpebral fissures had decreased considerably by adulthood (76% vs 47%). Asymmetry, as captured by a difference in ICD and PFL ≥5 mm, was likewise somewhat decreased (46% vs 35%). Clinical presentations with asymmetrical growth pattern can raise concerns about FASD in addition to other genetic syndromes.[54] Although the correlation between OFC and PFL has been assumed to be strong,[55] the variance in PFL, explained by OFC where studied, is at best 15%.[56] Whereas brain growth drives the growth of the head, PFL is better understood as related to factors other than crude brain size, such as growth of the eye[56] and the forebrain.[57] The correlation between ICD and PFL in patients with FASD has been weak,[55] and ICD may therefore capture aspects of neurodevelopment not captured by PFL.

Nonspecific somatic complaints have previously been reported in association with, and preceding, affective disorders,[58] both of which were common in this cohort. The heritability of affective disorders has been estimated to be 40%.[59] Given that alcohol abuse sometimes indicates self-medication,[60] a genetic liability may be overrepresented in FASD independently of the alcohol exposure itself. In addition, traumatic experiences in childhood, academic and professional failure, and underachievement relative to peers pose an environmental substrate for demoralization and chronic stress, increasing liability for affective disorders.[59]

The rates of depression, anxiety disorders and suicide attempts found in this cohort correspond to findings of earlier studies.[35,39,61] Executive dysfunction and marked attention problems have been highlighted elsewhere[17,35] but this is, to our knowledge, the first study in adults with FASD assessing criteria for ADHD. The increase in ADHD from childhood (62%) to adulthood (70%) may reflect both parents' tolerance for executive dysfunction in childhood and increased demands on executive function in adulthood. However, lower symptoms of impulsivity and less deviant social interactions in adulthood, based on standardized testing, could lead researchers to overestimate the functioning of adults with FASD, a point reiterated by researchers in the field of FASD.[17,62]

In this cohort, psychotic disorders were rare (3%), which is in contrast to results by Famy et al,[63] who report mainly brief psychotic disorder, in 40% of 25 studied individuals with FASD. The relation between psychotic disorders and substance dependence in that sample is not discussed. The rate of depression (44% vs 42%) and psychiatric disorders in general (92% vs 88%) was similar.

Mukherjee et al[64] compared children with FASD exposed (n=45) and not exposed (n=52) to prolonged neglect, and found no significant difference in neurodevelopmental morbidity. They concluded from their sample that alcohol exposure and innate factors explain neurodevelopmental morbidity alone, independently of neglect. This is in line with a recent twin study, where monozygotic twins, despite being differentially exposed to childhood maltreatment, were concordant regarding symptom rates of neurodevelopmental disorders.[65] In a longitudinal study of English and Romanian adoptees, by Sonuga-Barke et al, two cohorts who spent >6 months vs <6 months in an institution were compared. Rates of emotional distress (45% vs 18%) and ADHD symptoms (32% vs 12%) were higher in the group with prolonged institutionalization.[66] Despite higher rates of extremely low birth weight <2500 g (32.9% vs 22%) in the group with the prolonged stay, and limited reports of

perinatal risks such as gestational age, alcohol exposure, birth head circumference, or any dysmorphology assessment during the study, the difference in neurodevelopmental outcome was attributed mainly to institutional deprivation. It is worth noting that 30% of the initial cohort in our study were adoptees from Romania, born in the same years as the participants in Sonuga-Barke et al's cohort',[22] but generally adopted at a later age (mean age 3.3 years). Given the high minimum rate of confirmed alcohol exposure in our initial sample (52%), and the fact that institutions prioritize healthier children for internal adoptions at a young age, a bias towards higher rates of alcohol exposure may be a substantial source of confounding in their group of adoptees.[66]

A review by Kable et al summarizes the literature on neurobehavioral deficits in FASD, specifically deficits in neurocognition, self-regulation, and adaptive behavior.[62] A characteristic of FASD is increasing adaptive deficits with age, relative to peers. A higher than expected rate of autism has been reported previously in FASD,[67,68] and deficits in social skills and communication are part of the adaptive deficits described. Adult adaptive functioning requires goal-directed behavior, abstract thinking, generalization of cause and effect, managing household, finances, and social relations – all functions that are inseparable from neurocognition and self-regulation. The decrease in non-verbal IQ to adulthood indicates that stunted growth in FASD applies not only to weight and length, but also to brain maturation and function, and corresponds to the adaptive deficits. To our knowledge, this marked decrease in IQ has not previously been demonstrated in the literature on FASD. The non-verbal tests cover spatial reasoning, working memory, problem solving, logical reasoning, and generalization, higher order functions requiring efficient interconnectivity of large brain areas.[69] An underlying deficit in these higher order brain functions would be expected to affect proficiency in complex tasks in general, not just one, becoming more evident with age.

Conclusions

Children with FASD have a prenatal brain injury, often associated with compounding effects from postnatal deprivation and unstable social circumstances. These children require rehabilitation, special education and social support. This is accomplished by assessment and care by pediatricians, psychologists, allied health professionals, and teachers, beginning in childhood and across the lifespan.

Figure 1. Diagnostic domains of fetal alcohol spectrum disorders in childhood and young adulthood in 37 adoptees

Figure 2. Anthropometric measurements at four time points for 21 adoptees with fetal alcohol syndrome

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Valdemar Landgren collected data, carried out initial analyses, and drafted the initial manuscript.

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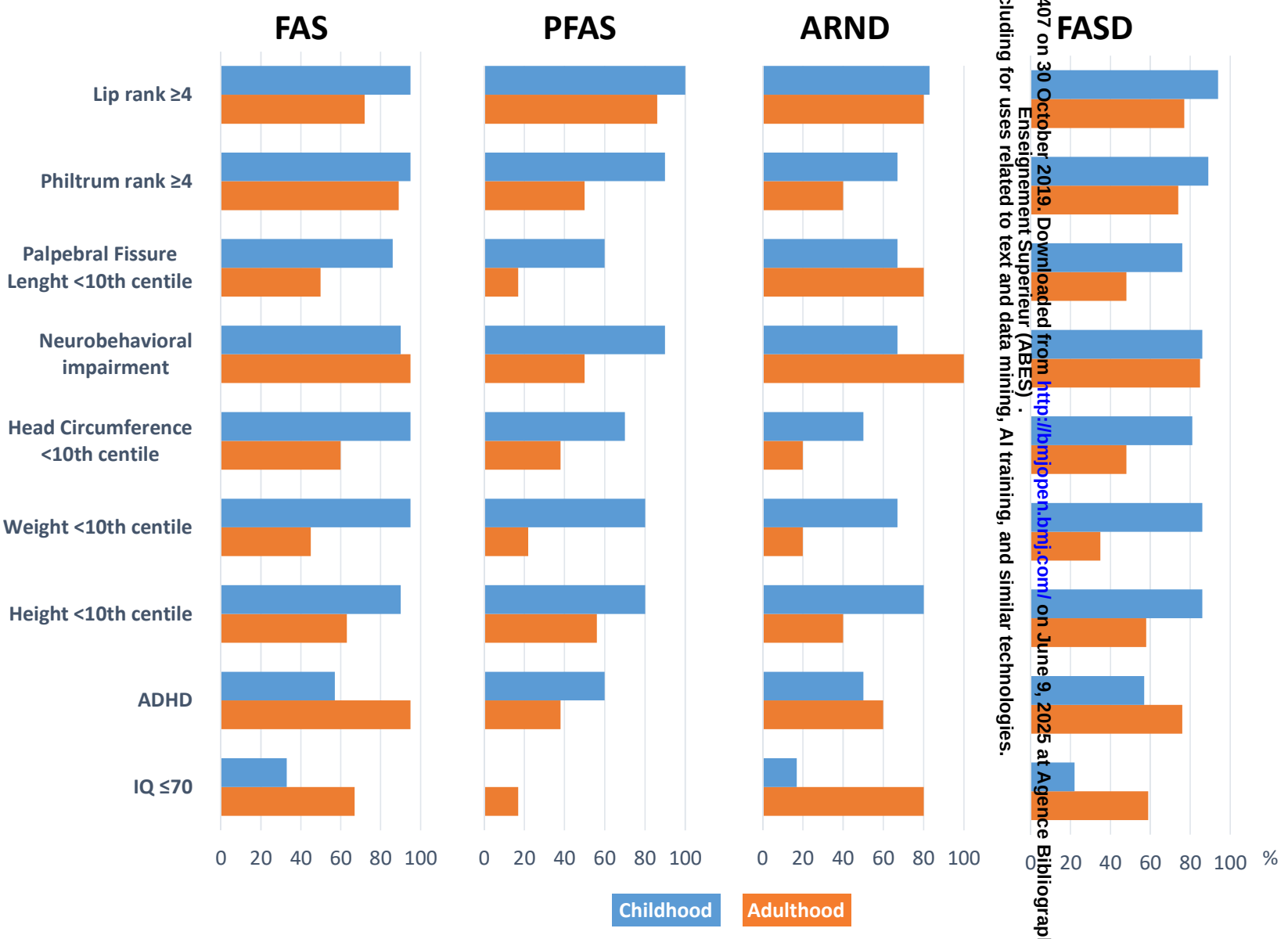

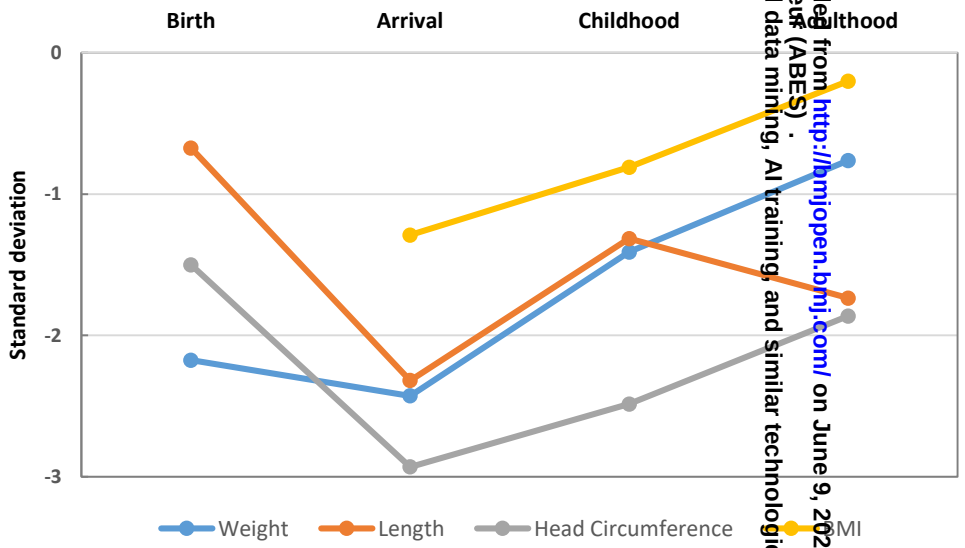

Supplementary Appendix S1 – Clinical Vignettes

The CGI-S was developed to capture clinical impressions of patients participating in clinical trials of psychiatric disorders that transcend mere symptom checklists. It has been utilized together with the impression of improvement (CGI-I) scores from the therapy under study. The CGI-S measures overall function and symptom severity on an ordinal scale from 1 to 7. The scoring rationale of the CGI-S may differ between diseases and trials. For the purpose of this study, the scoring was adapted from the guidelines of Busner et al, where 1 = "normal," 2 = "borderline mentally ill," 3 = "mildly ill" (with minimal impairment), 4 = "moderately ill" (warrants medication), 5 = "markedly ill" (has significantly impaired occupational function), 6 = "severely ill" (requires assistance from others), and 7 = "extremely ill" (may be hospitalized). Clinical vignettes for each score are presented below. In the vignettes, some identifying details have been changed to protect the privacy of individuals.

CGI 1 – Normal:

A woman with ADHD and PFAS at index evaluation completed 12 years of school and 2 years of post-secondary qualified education. She has a history of suicide attempt as a teenager, but exhibits no psychopathology upon evaluation. She medicates for generalized epilepsy. Her current IQ is 102, and her ABAS-II score 114. She lives with a partner and holds a regular job.

CGI 2 – Borderline mentally ill:

A woman with ADHD, DCD, oppositional defiant disorder (ODD), and ARND at index evaluation completed 12 years of school and 2 years of qualified vocational education. She has a history of suicide attempt as a child, and exhibits symptoms of hyperactivity, but no present ADHD or other psychopathology upon evaluation. Her current IQ is 63, andher ABAS-II score 116. She lives independently and holds a regular job.

CGI 3 – Mildly ill:

A man with microcephaly, ADHD, DCD, ODD, and FAS at index examination who completed 12 years of regular school. He reports a history of depression and screens positive for agoraphobia, post-traumatic stress disorder (PTSD), and persistent ADHD. His IQ is 62, his ABAS-II score 92. He lives with her parents and attends an adult education college.

CGI 4 – Moderately ill:

A woman with DCD, ODD, and ARND at index examination attended school for 12 years. She is studying to get her school grades as mental health issues in her teenage years had prevented her from obtaining them while at school. She reports a history of depression, screens positive for ADHD (inattentive type), and medicates with antidepressants. Her IQ is 62 andher ABAS-II score 64. She has not held a job, and lives with her sibling.

CGI 5 – Markedly ill:

A woman with partial cognitive dysfunction, DCD, and ARND at index. She has completed 12 years of schooling at a school for intellectually disabled children. She exhibits no psychopathology upon evaluation and has no medication. Her IQ is 58, and her ABAS-II score 114. She lives with a partner and has a son. She has regular contact with his adoptive parents, receives assistance for management of personal finances, and holds a government-supported internship at a store.

CGI 6 – Severely ill:

A man with mild intellectual disability, ADHD, and FAS at index examination who has received education for the intellectually disabled. He has persistent ADHD, screens positive for bulimia and PTSD, reports a history of depression, self-harm, suicide attempt, and rape, and has several pain problems. His IQ is 56, andhis ABAS-II score 48. He has no medication, lives alternately in supportive housing and with his adoptive parents, and receives permanent financial support.

CGI 7 – Extremely ill:

A woman with mild intellectual disability, epilepsy, ADHD, and FAS at index examination who has received education for the intellectually disabled. She has persistent ADHD and medicates for epilepsy and behavioral dysfunction. Her IQ is 36, and her ABAS-II score 46. She lives in a group home and receives permanent financial support.

Supplementary Table I S2. Ophthalmological Assessments in Adoptees with Fetal Alcohol Spectrum Disorders in Childhood and Young Adulthood

	Childhood (n=37)	Adulthood (n=29)[a]
Palpebral fissure length		
Right eye, median, mm (range)	25 (21–29)	29 (24–32)
Left eye, median, mm (range)	25 (21–29)	29 (24–32)
Mean z-score (SD)	-1.6 (0.9)	-1.4 (1.7)
Inner canthal distance		
Median, mm (range)	29 (24–35)	32 (26–37)
Mean z-score (SD)	-0.2 (1.2)	0.0 (1.2)
ICD≥5–10 mm>PFL[b], n (%)	17 (46)	10 (35)

Z-scores are calculated according to Hall et al.[29]

[a]Of 30 examined, outer ocular measurements were missing in one case.

[b]ICD≥5–10mm>PFL is defined as a difference of ≥5 mm between the inner canthal distance (ICD) and the length of the smallest palpebral fissure (PFL) in the same individual.

Supplementary Table II S3. Psychological Assessments of Adoptees with Fetal Alcohol Spectrum Disorders in Childhood and Young Adulthood

Intellectual Quotient		n
Childhood	86 (50–107)	37
Adulthood	71 (36–121)	29
>85	3 (10)	
70-85	7 (24)	
<70	19 (66)	
Leiter-R scores regarding cognitive and social abilities rated by the psychologist		
Childhood	85 (66–106)	37
Adulthood	89 (81–110)	29
>85[a]	24 (83)	
<85[b]	5 (17)	
Adaptive behavior assessment scores in adulthood rated by parents		26
Cognitive function	65 (40–114)	
Social function	65 (50–112)	
Practical function	78 (58–120)	
General abilities	66 (40–120)	

Data is presented as median (range) or numbers (percentage) as appropriate.

[a]One out of five was on ADHD medication.

[b]Six out of 24 were on ADHD medication.

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3

Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of	6-8

		assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	9
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	9
Statistical methods	#12c	Explain how missing data were addressed	N/A because statistical analyses and comparisons were not part of aims
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	N/A
Statistical methods	#12e	Describe any sensitivity analyses	N/A

Results

Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	6, 9
Participants	#13b	Give reasons for non-participation at each stage	9
Participants	#13c	Consider use of a flow diagram	Text on page 6 and 9
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	tables
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	tables
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	9
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	N/A
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision	N/A

		(eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	N/A
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	15
Discussion			
Key results	#18	Summarise key results with reference to study objectives	16
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	16
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	16-22
Generalisability	#21	Discuss the generalisability (external validity) of the study results	16
Other			

Information

Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24