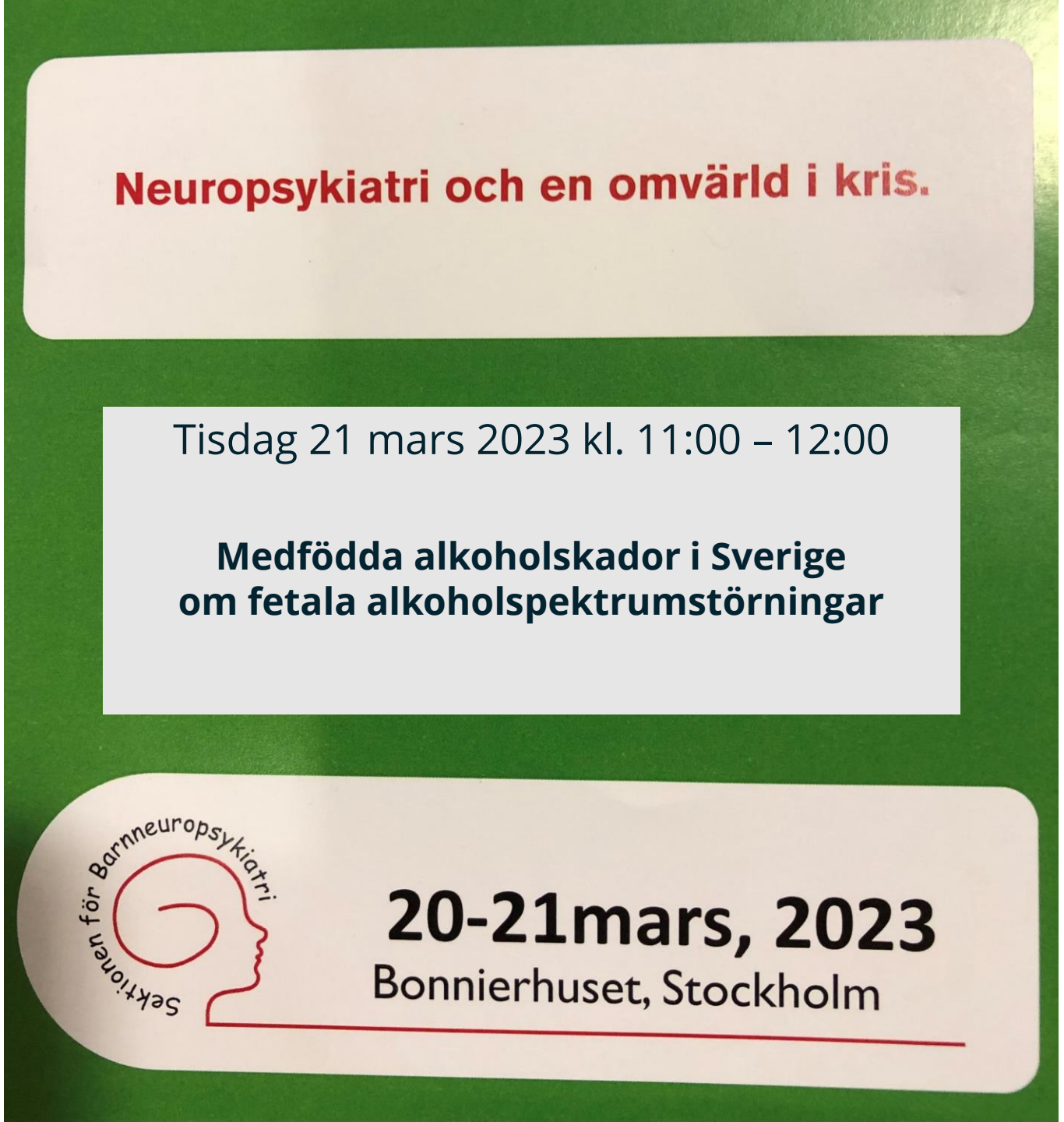
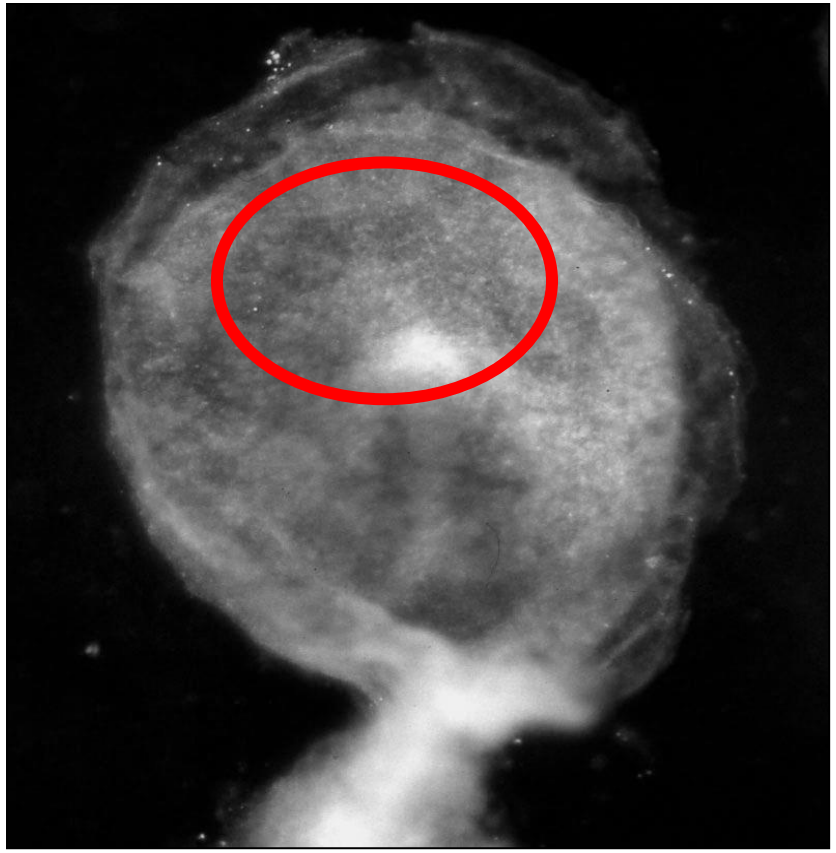
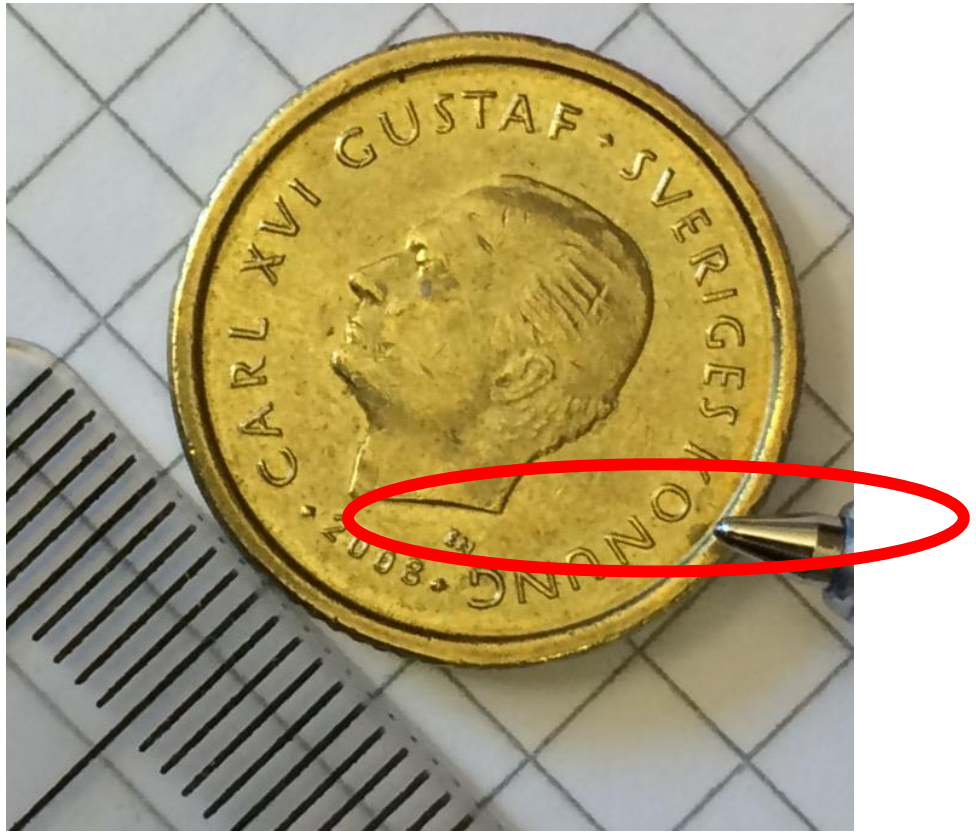

Neuropsykiatri och en omvärld i kris.
Tisdag 21 mars 2023 kl. 11:00 – 12:00
Medfödda alkoholskador i Sverige
om fetala alkoholspektrumstörningar
Sektionen för Barnneuropsykiatri
20-21mars, 2023
Bonnierhuset, Stockholm

Vad ryms i O:et -KONUNGEN?

I mitten på tredje veckan postkonception är människoembryot en liten skiva, några celler tjock och med en diameter på c:a 0,5 mm och ryms i bokstaven O i Carl XVI GUSTAF SVERIGES K**O**NUNG . Hjärnan, ögon och ansikte har redan börjat utvecklas.






Beroende med stor problemtyngd
50 000
Beroende med låg till måttlig problemtyngd
250 000
Skadligt bruk/missbruk
300 000
Högkonsumtion utan aktuella problem
450 000
Inga alkoholproblem
6,5 miljoner svenskar >15 års ålder

Alfred E Neuman ansiktet

Livet är kort, konsten är lång, rätta tillfället flyktigt,
erfarenheten bedräglig, omdömet svårt.
Hippokrates

Finns FAS på BUP?

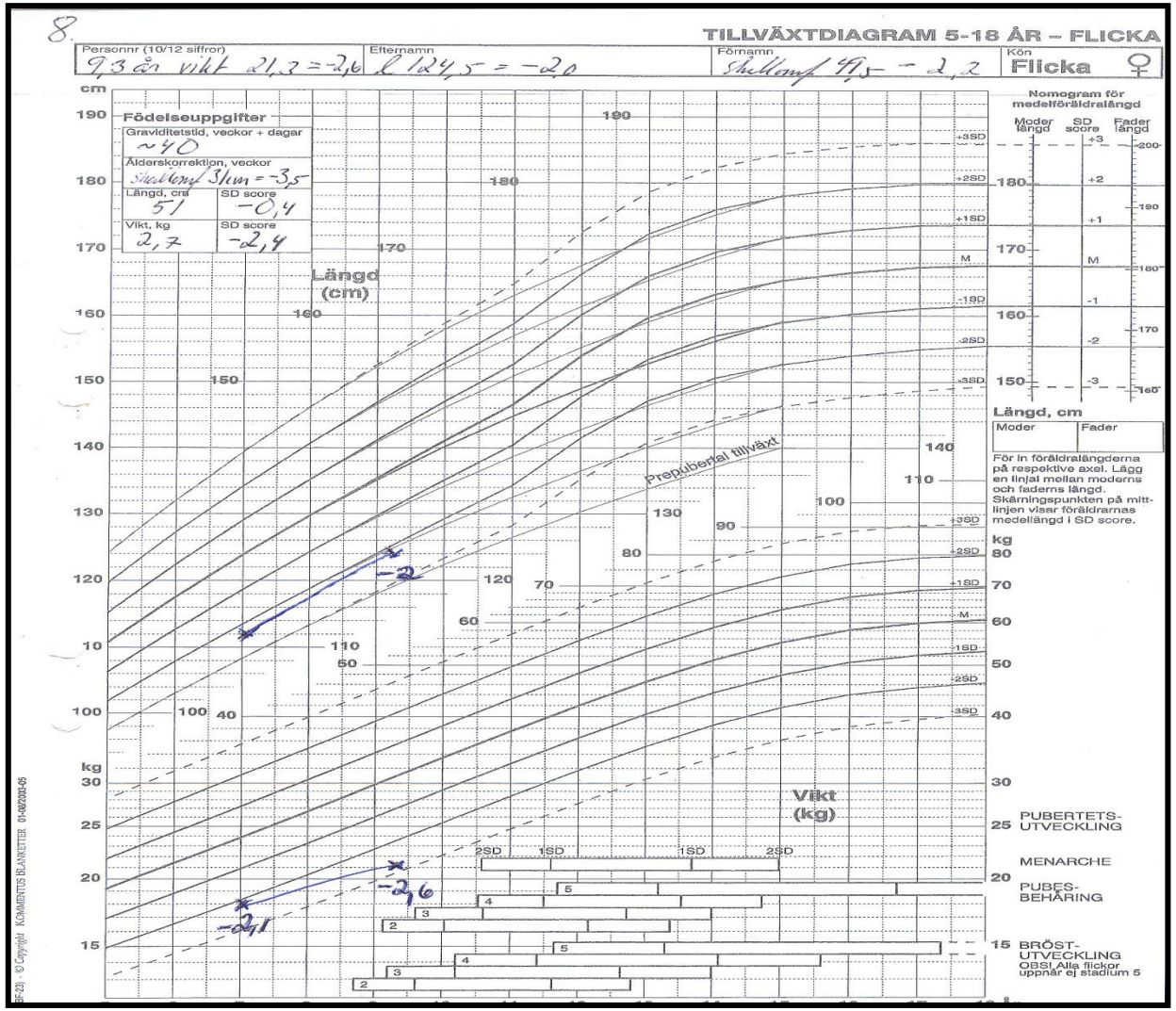
Finn(s) FAS i skolan ! (?)

Finn(s) FAS på Skas ! (?)

FAS förbisedd

vad är fetalt alkoholsyndrom - FAS?

- FAS är ett fosterskadesyndrom orsakat av alkohol som karaktäriseras av:
  - Ansiktsdysmorfologi
  - Tillväxtstörning
  - CNS-skada
- FASD (FASS) Fetala Alkohol Spektrum Störningar
- FAS är en etiologisk diagnos
- Alkohol är en teratogen substans


8.
TILLVÄXTDIAGRAM 5-18 ÅR – FLICKA
Personnr (10/12 siffror)
9,3 år vikt 21,3 = -2,6
Efternamn
l 124,5 = -2,0
Förnamn
Skellemf 49,5 = -2,2
Kön
Flicka
Födelseuppgifter
Graviditetstid, veckor + dagar
~40
Ålderskorrektion, veckor
Skellemf 3/um = -3,5
Längd, cm
51
SD score
-0,4
Vikt, kg
2,7
SD score
-2,4
Längd (cm)
Prepubertal tillväxt
Vikt (kg)
-2
-2,6
-2,1
Nomogram för medelföräldralängd
Moder längd
SD score
Fader längd
Längd, cm
Moder
Fader
För in föräldralängderna på respektive axel. Lägg en linjal mellan moderns och faderns längd. Skärningspunkten på mittlinjen visar föräldrarnas medellängd i SD score.
PUBERTETS-UTVECKLING
MENARCHE
PUBES-BEHÅRING
BRÖST-UTVECKLING
OBS! Alla flickor uppnår ej stadium 5
© Copyright KOMMENTUS BLANKETTER 04-6820205-05

Development of length, weight and head circumference from birth, arrival and 5 years after arrival

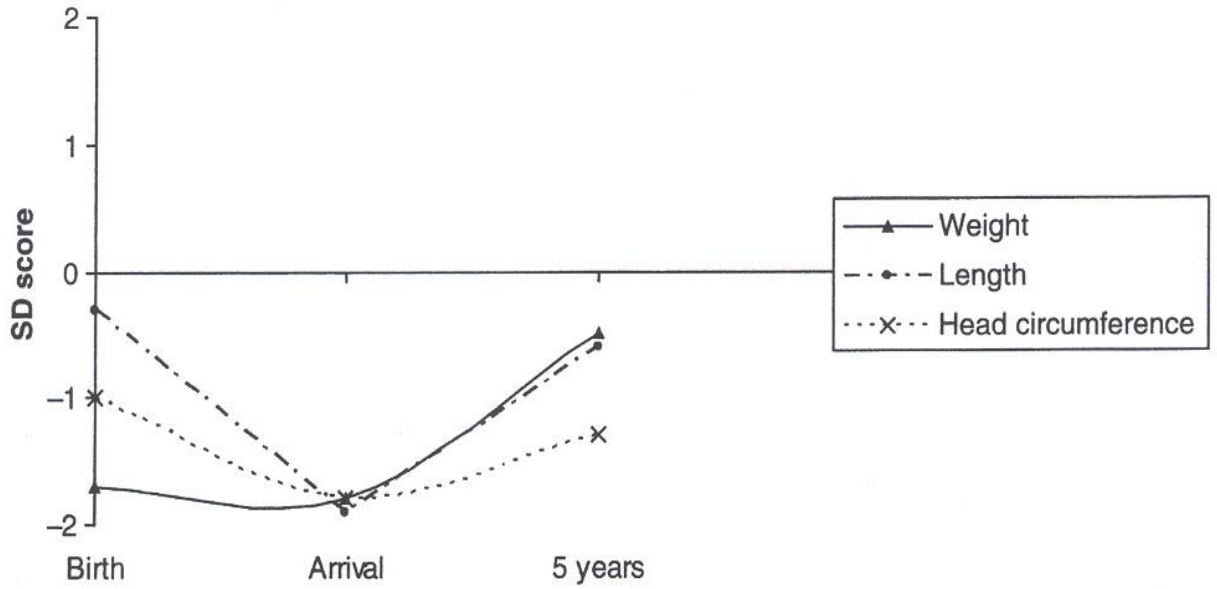


Figure 1. Weight, length and head circumference in 76 children in Sweden adopted from Eastern Europe. Measurements, in standard deviation scores (SDSs) at birth, arrival and follow-up.

Landgren et al 2010 Prenatal Alcohol exposure and Neurodevelopmental Disorders in children adopted from Eastern Europe
Pediatrics 2010; 125:1178-85

5 yrs after adoption, 8 yrs of age

Prenatal Alcohol Exposure and Neurodevelopmental Disorders in Children Adopted From Eastern Europe

WHAT'S KNOWN ON THIS SUBJECT: Adoption brings environmental improvement over an institutional upbringing in the country of birth. Alcohol is a teratogen that causes a spectrum of malformations and neurologic, cognitive, and behavioral deficits that are fully preventable.

WHAT THIS STUDY ADDS: FASDs were extremely common in a follow-up study of children adopted from eastern Europe. Children with FASDs often (88%) had comorbid neurodevelopmental/cognitive disorders. Familiarity with diagnostic guidelines for FASDs is essential for assessment and treatment.

abstract

OBJECTIVES: The purposes of this investigation were to determine the frequencies of and associations between different neurodevelopmental disorders and to study the potential lasting effects of alcohol on children adopted from eastern Europe.

METHODS: In a population-based, prospective, observational, multidisciplinary, cross-sectional, cohort study of 71 children adopted from eastern Europe, children were assessed 5 years after adoption, from pediatric, neuropsychological, and ophthalmologic perspectives.

RESULTS: Fetal alcohol spectrum disorders, that is, fetal alcohol syndrome (FAS), partial FAS, and alcohol-related neurodevelopmental disorders, were identified for 52% of children; FAS was found for 30%, partial FAS for 14%, and alcohol-related neurodevelopmental disorders for 9%. Alcohol-related birth defects were found for 11% of children, all of whom also were diagnosed as having FAS. Mental retardation or significant cognitive impairment was found for 23% of children, autism for 9%, attention-deficit/hyperactivity disorder for 51%, and

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KEY WORDS

fetal alcohol syndrome, autism, attention-deficit/hyperactivity disorder, developmental coordination disorder, adopted children, mental retardation, microcephalus, ocular malformations

ABBREVIATIONS

ADHD—attention-deficit/hyperactivity disorder
ARBD—alcohol-related birth defect
ARND—alcohol-related neurodevelopmental disorder
DCD—developmental coordination disorder
DSM-IV—Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
FAS—fetal alcohol syndrome
FASD—fetal alcohol spectrum disorder
IOM—Institute of Medicine
WISC-III—Wechsler Intelligence Scale for Children, Third Revision
PFAS—partial fetal alcohol syndrome
OFC—occipitofrontal circumference

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doi:10.1542/peds.2009-0712
Accepted for publication Jun 21, 2010

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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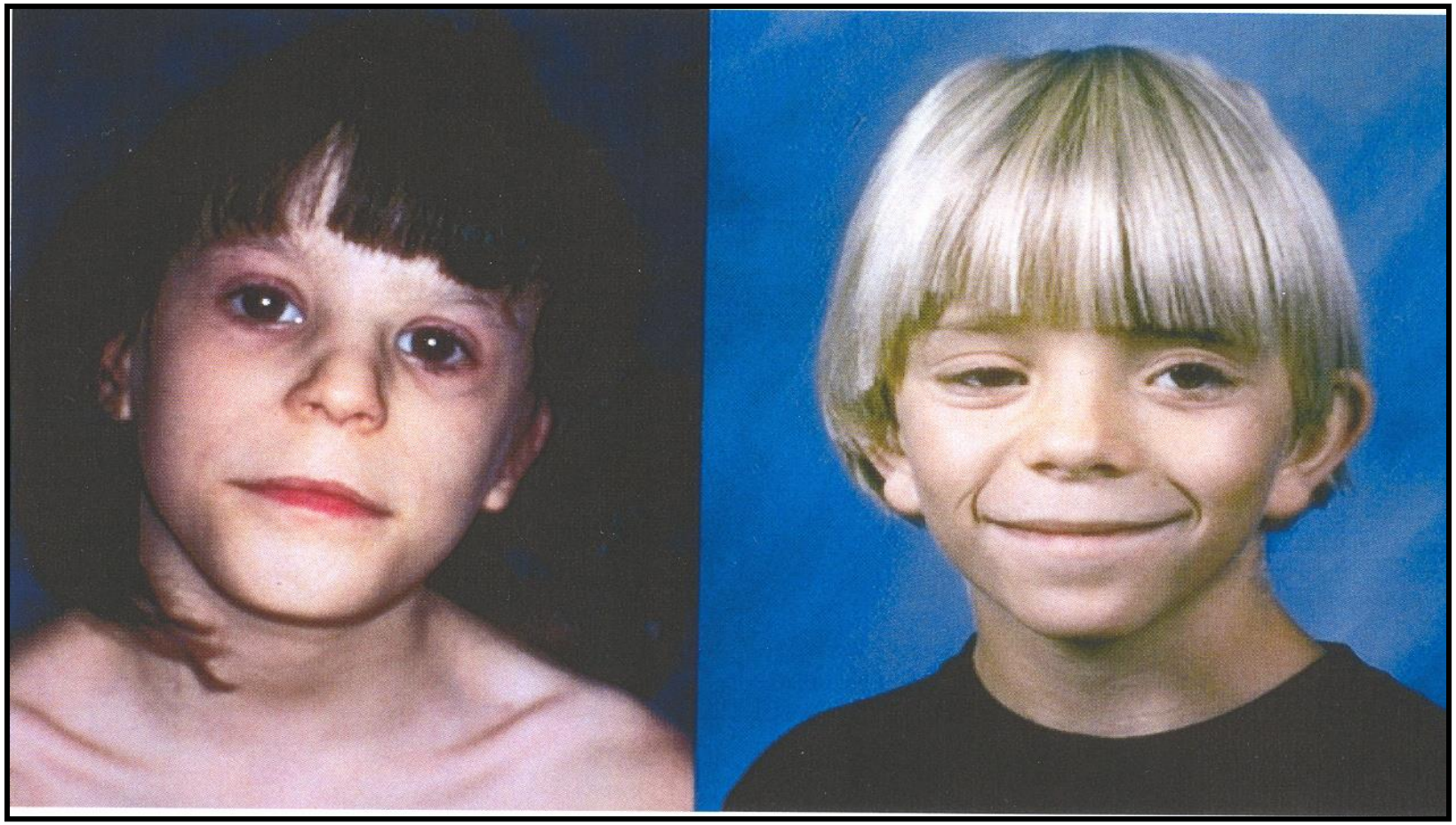
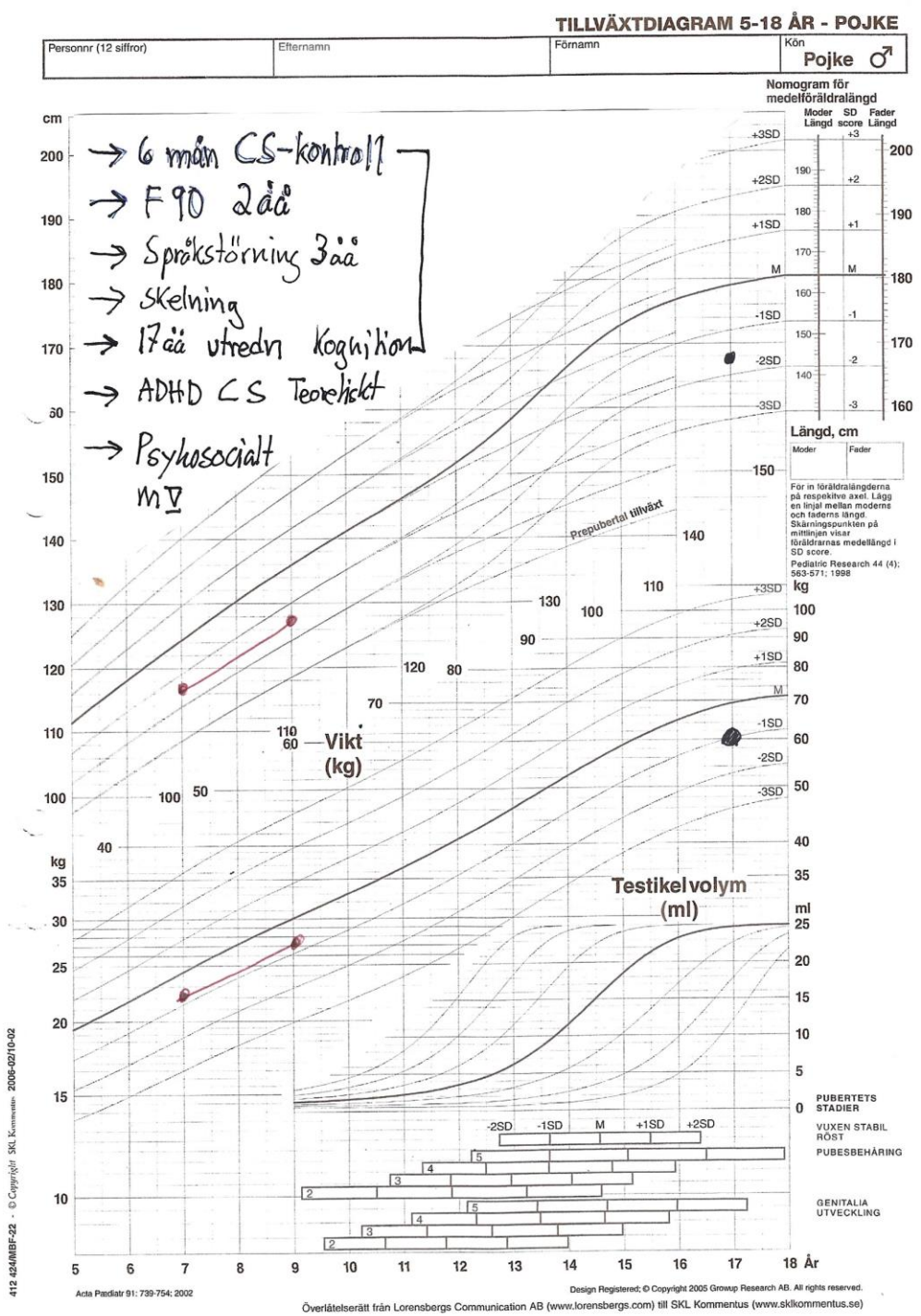
- <u>Etiological diagnosis</u>
- FASD 52%
- FAS (n=21) 30%
- PFAS 14%
- ARND 9%
- ARBD 11%

Har den här flickan en hjärnskada?

ansiktsavvikelser





Kognition enligt WISC V		ADAPTATION enligt ABAS Fä/Lä	
V i	p 95	Kognition i	67–75/85–95
Vsi	p 26	Socialt i	61–71/88–100
Fi	p 36	Praktiskt i	74–82/82–100
Si	p 5	GAF	68–72/82–90

Noteringar i utredningen

”upplevs smart”

”Behöver särskilt stöd i teoretiska ämnen”

”kan inte hantera pengar”

SRS - empatibrist

1) Exponerad
2) l ~ -1,8 V ~ -1
3) LPH 5/5
4) hvomf. ~ p3
Kognition

TILLVÄXTDIAGRAM 5-18 ÅR - POJI

Förnamn | Kön: Pojke

Nomogram för medelföräldralängd

Längd (cm)

Vikt (kg)

Testikelvolym (ml)

Prepubertal tillväxt

Längd, cm

Moder | Fader

Pubertets stadier

Vuxen stabil röst

Pubesbehåring

Genitalia utveckling

Growup

Acta Paediatr 91: 739-754; 2002

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TABLE 1 Updated Criteria for the Diagnosis of FASD

Diagnostic Categories

(See Table 2 for definition of documented prenatal alcohol exposure)

I. FAS

(With or without documented prenatal alcohol exposure)

A diagnosis of FAS requires all features, A–D:

A. A characteristic pattern of minor facial anomalies, including ≥2 of the following:
   1. Short palpebral fissures (≤10th centile)
   2. Thin vermilion border of the upper lip (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
   3. Smooth philtrum (rank 4 or 5 on a racially normed lip/philtrum guide, if available)

B. Prenatal and/or postnatal growth deficiency
   1. Height and/or weight ≤10th centile (plotted on a racially or ethnically appropriate growth curve, if availabl

C. Deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology, including ≥1 of the followin
   1. Head circumference ≤10th percentile
   2. Structural brain anomalies
   3. Recurrent nonfebrile seizures (other causes of seizures having been ruled out)

D. Neurobehavioral impairment[a]
   1. For children ≥3 y of age (a or b):
      a. WITH COGNITIVE IMPAIRMENT:

—Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verb

OR

—Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific visual-spatial impairment)

      b. WITH BEHAVIORAL IMPAIRMENT WITHOUT COGNITIVE IMPAIRMENT:

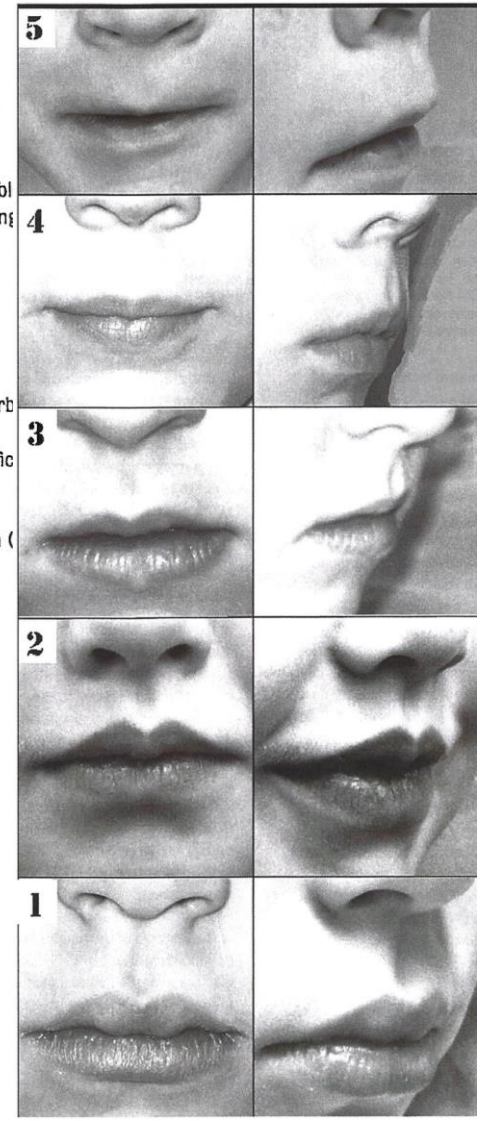
—Evidence of behavioral deficit in at least 1 domain ≥1.5 SD below the mean in impairments of self-regulation (attention deficit, or impulse control)

   2. For children <3 y of age:

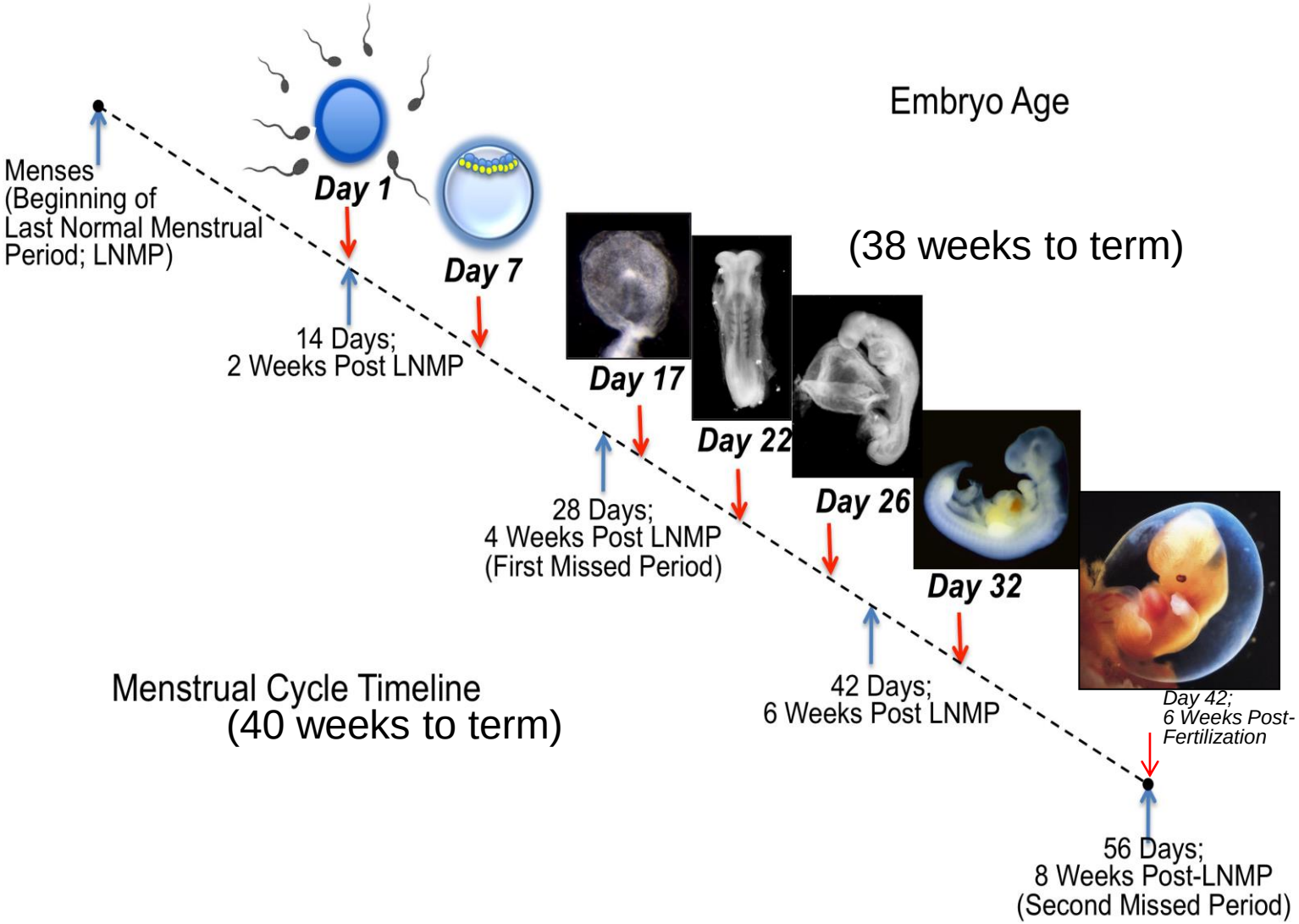
—Evidence of developmental delay ≥1.5 SD below the mean

ICD10: Q86.0

North American White Lip/Philtrum Guide



Much of Human Embryogenesis occurs Prior to the time that Pregnancy is Typically Recognized



Teratologi
om missbildningar, orsaker, mekanismer, och utvecklingsavvikelser, funktionellt och strukturellt

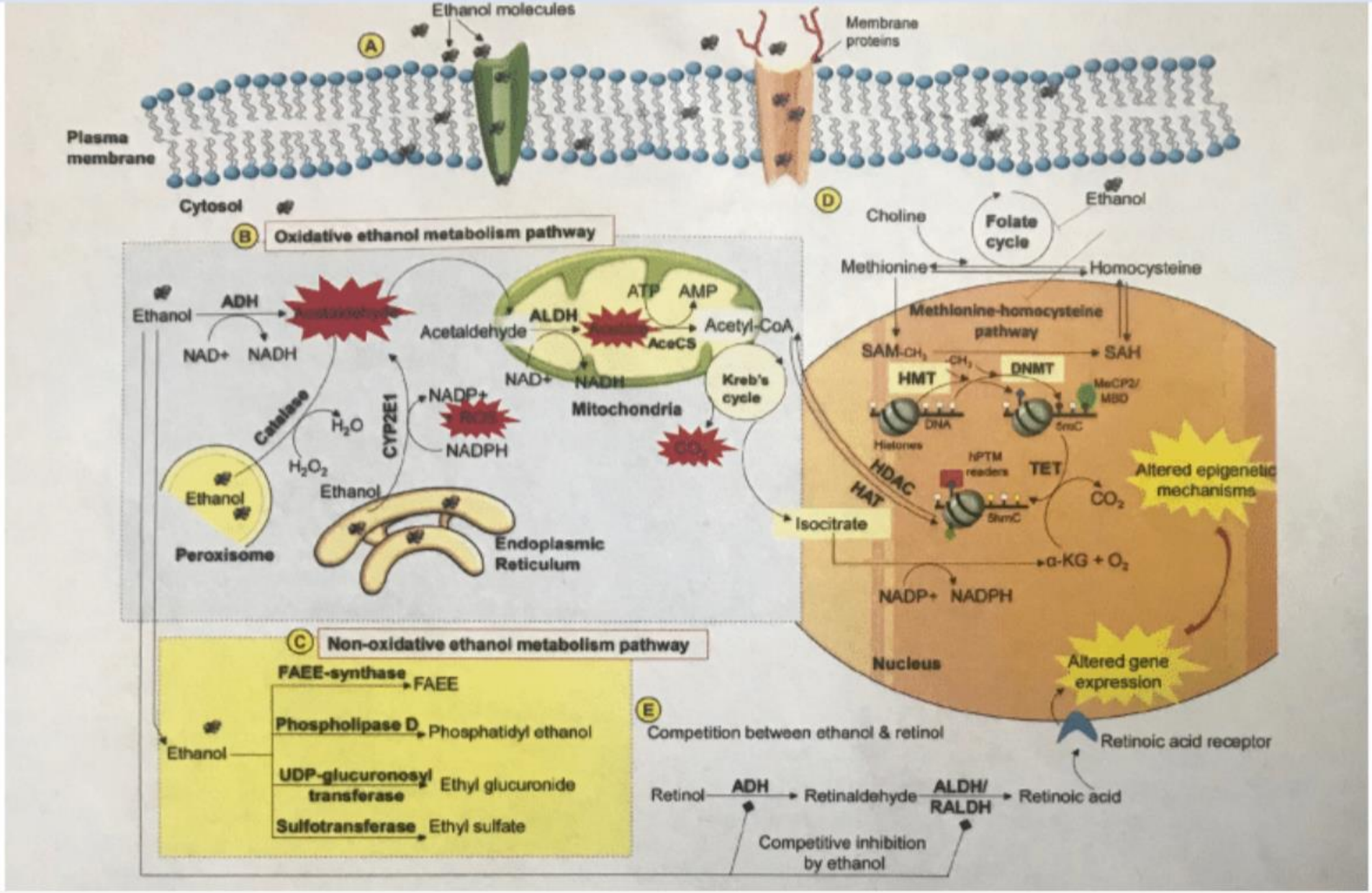
- **Orsaker**
- Djurstudier början av 1900-talet (röntgenstrålar, dieter)
- 1937 hormoner
- 1941 virus
- 1952 aminopterin
- 1959 Metylkvicksilver Minamata 1956-59 avloppsvatten, fisk
- 1961 Talidomid embryopati, fokomelier, sk
- Bly
- 1973 Alkohol (Etanol) FAS Jones and Smith

Vetenskaplig teratologi
studerar orsaker och mekanismer bakom miljöeffekter på germinalceller, embryon, foster och omogna individer (Wilson 1973)

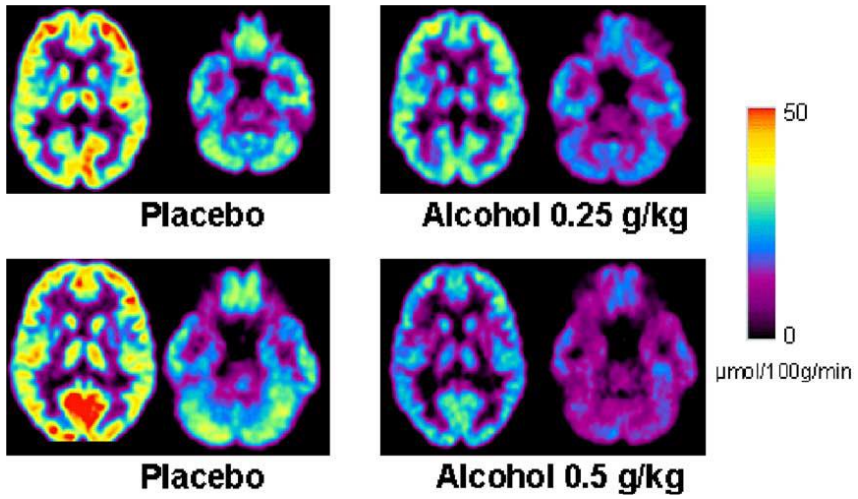
- **Orsaker:** Genetiska och miljömässiga
- **Sex principer:**
- Genetisk predisposition
- Utvecklingsmässigt stadium
- Fostergiftets verkningsmekanism(-er)
- Toxinets tillgänglighet till vulnerabla vävnader
- Sluteffekt: död, missbildning, tillväxthämning, skada (impairement)
- Dos respons – effekt

Etanol:
lösningsmedel, rusmedel, desinfektionsmedel, mutagent
och teratogent
vattenlösligt och fettlösligt passerar alla biologiska membran

Från, Overview of the Genetic Basis and Epigentic Mechanisms that Contribute to FASD Pathobiology ; Current Topics of Medicinal Chemistry 2017



Alkoholinducerade effekter friska försökspersoner

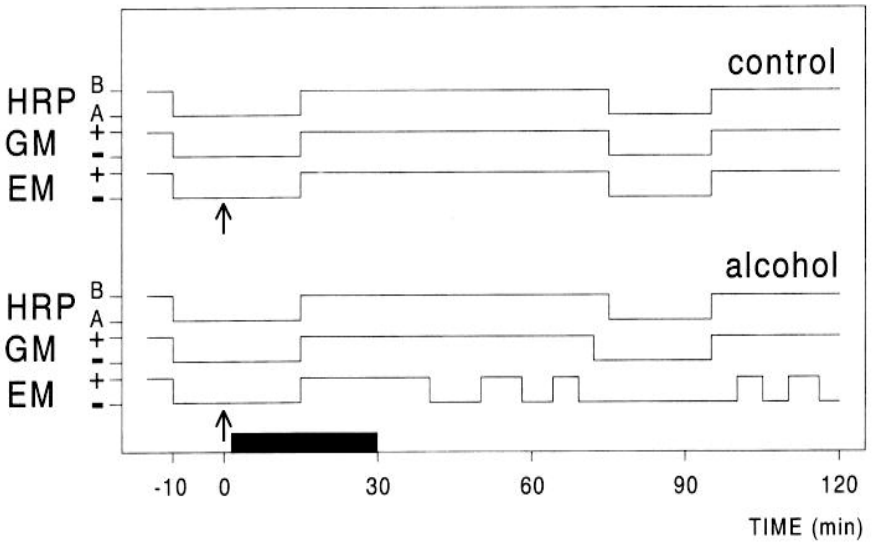


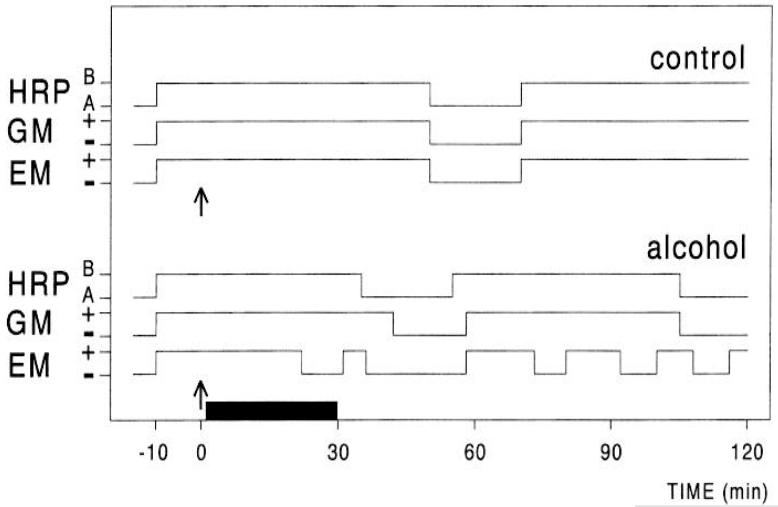
- 0.25g/alkohol/kg - över 40 min
- 0.5mg/kg – 2-3 standardglas

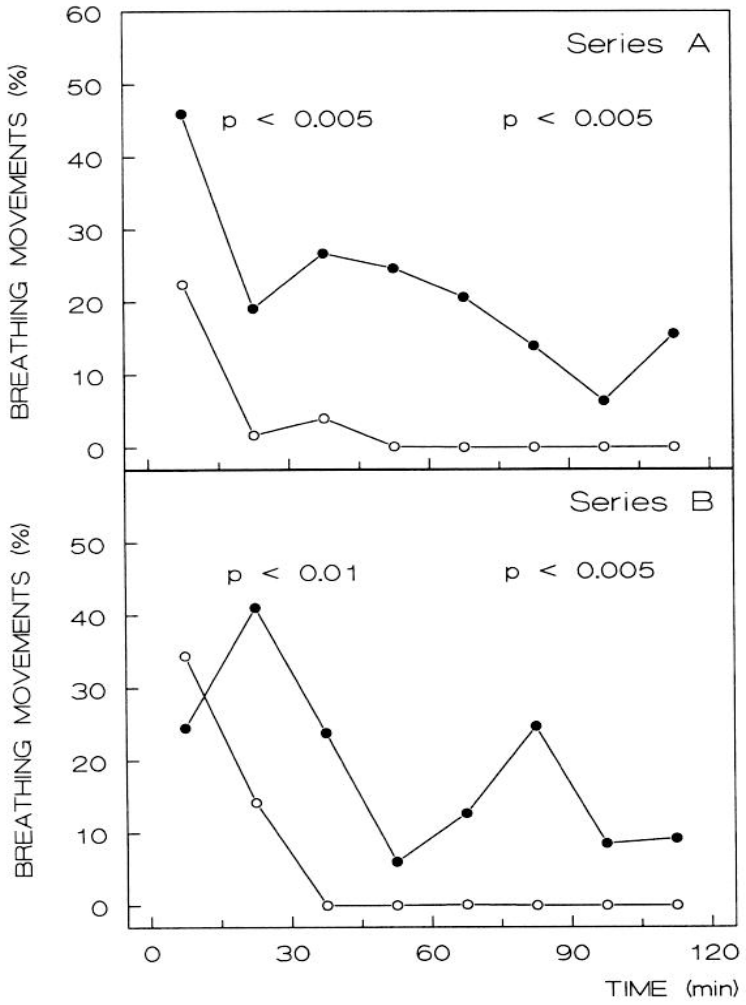
N.D. Volkow et al. / NeuroImage 29 (2006) 295– 301

Förändringar efter 2 glas vin

Mulder et al. Pediatric Research 1998







A Quite sleep; B active sleep

Orsak

- alkoholexponering under graviditet (1:a – 3:e trimestern)
- alkohol: passerar moderkakan,
- elimineras långsammare av fostret och
  - påverkar celldelning,
  - ökar förekomsten av fria radikaler,
  - påverkar tillväxtfaktorer,
  - skadar astrocyter,
  - påverkar celladhesion och axonutvecklingen,
  - ändrar biokemiska signaler,
  - undertrycker neuronal aktivitet och genuttryck samt kan utlösa apotos (celldöd). alkohol är ett teratogen, ett fostergift

Journal of Perinatology (2012) 32, 652–659

www.nature.com/jp

STATE-OF-THE-ART

Prenatal alcohol exposure, blood alcohol concentrations and alcohol elimination rates for the mother, fetus and newborn

L Burd, J Blair and K Dropps

North Dakota Fetal Alcohol Syndrome Center, Department of Pediatrics, University of North Dakota School of Medicine and Health Sciences, Grand Forks, ND, USA

Fetal alcohol spectrum disorders (FASDs) are a common cause of intellectual impairment and birth defects. More recently, prenatal alcohol exposure (PAE) has been found to be a risk factor for fetal mortality, stillbirth and infant and child mortality. This has led to increased concern about detection and management of PAE. One to 2 h after maternal ingestion, fetal blood alcohol concentrations (BACs) reach levels nearly equivalent to maternal levels. Ethanol elimination by the fetus is impaired because of reduced metabolic capacity. Fetal exposure time is prolonged owing to the reuptake of amniotic-fluid containing ethanol by the fetus. Alcohol elimination from the fetus relies on the mother's metabolic capacity. Metabolic capacity among pregnant women varies eightfold (from 0.0025 to 0.02 g dl^{-1} h^{-1}), which may help explain how similar amounts of ethanol consumption during pregnancy results in widely varying phenotypic presentations of FASD. At birth physiological changes alter the neonate's metabolic capacity and it rapidly rises to a mean value of 83.5% of the mother's capacity. FASDs are highly recurrent and younger siblings have increased risk. Detection of prenatal alcohol use offers an important opportunity for office-based interventions to decrease exposure for the remainder of pregnancy and identification of women who need substance abuse treatment. Mothers of children with FAS have been found to drink faster, get drunk quicker and to have higher BACs. A modest increase in the prevalence of a polymorphism of alcohol dehydrogenase, which increases susceptibility to adverse outcomes from PAE has been reported. Lastly, detection of alcohol use and appropriate management would decrease risk from PAE for subsequent pregnancies.

Journal of Perinatology (2012) **32**, 652–659; doi:10.1038/jp.2012.57; published online 17 May 2012

Keywords: *ethanol; fetal; exposure; maternal; metabolism; newborn*

Correspondence: Dr L Burd, North Dakota Fetal Alcohol Syndrome Center, Department of Pediatrics, University of North Dakota School of Medicine and Health Sciences, 501 North Columbia Road, Grand Forks, ND 58203, USA.
E-mail: larry.burd@med.und.edu
Received 6 December 2011; revised 29 March 2012; accepted 30 March 2012; published online 17 May 2012

Introduction

Ethanol is a well-known fetal teratogen, which can cause a range of pathophysiological consequences termed fetal alcohol spectrum disorder (FASD). It is likely that both the duration of teratogen exposure and dosimetry have an important role in the development of FASD. Understanding the maternal, fetal and neonatal alcohol elimination rates (AER) and the mechanisms of elimination is important for management of ethanol exposure in the fetus and neonate.

Prenatal alcohol exposure (PAE) is a pandemic health problem. In the United States, the prevalence of alcohol use by non-pregnant women during their childbearing years was 54.6% in 2001.[1] Approximately 50% of pregnancies in the United States are unplanned, and therefore many will have early exposure before pregnancy can be confirmed.[2]

In 2001, 12.5% of pregnant women reported at least some alcohol use during their pregnancy and 1.6% reported frequent use of alcohol while pregnant.[1] As a result, for the four million pregnancies each year in the United States, 500 000 have experienced some level of PAE and 64 000 had high levels of exposure. Current prevalence estimates of FASD from worldwide studies of school-age-children range from 20 to 50 per 1000 live births.[3] Current prevalence estimates of FASD within the US range from 0.5 to 9.1 cases for every 1000 live births.[3,4] Siblings of children with FASD have an increased rate for FASD.[5,6] Fetal alcohol syndrome (FAS) is the most readily identifiable category of FASD. In 2010, the prevalence of FAS in the United States was reported to be 0.2–1.5 cases per 1000 live births,[7] a review paper of more recent studies reports rates of FAS of 2 to 7 per 1000 live births.[3] This would equate to an annual incidence of FAS between 8000–28 000 cases each year in the United States alone.[7]

There is an association between maternal consumption of alcohol and unsuccessful pregnancies. Approximately 15% of all pregnancies end in spontaneous abortion, but among heavy drinking mothers the prevalence increases to 45%.[8] The occurrence of stillbirth among pregnancies exposed to ethanol has been shown

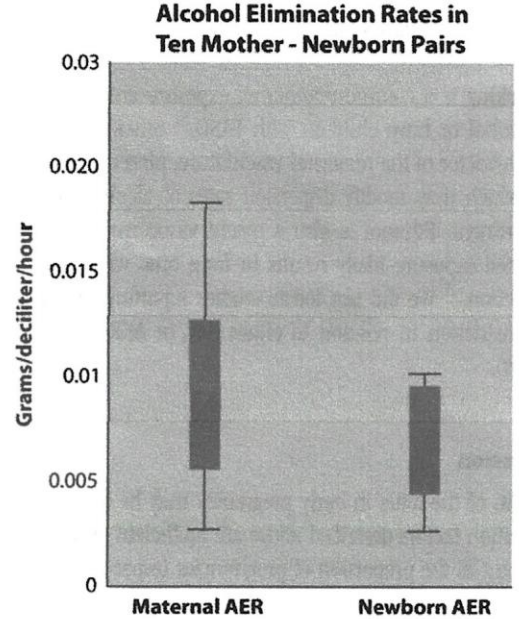


Figure 3 Midline of bar indicates mean value; ends of each bar indicate s.d.; the ends of the whiskers indicate the high and low values for the AER for the same 10 mother-newborn pairs in Figure 2.

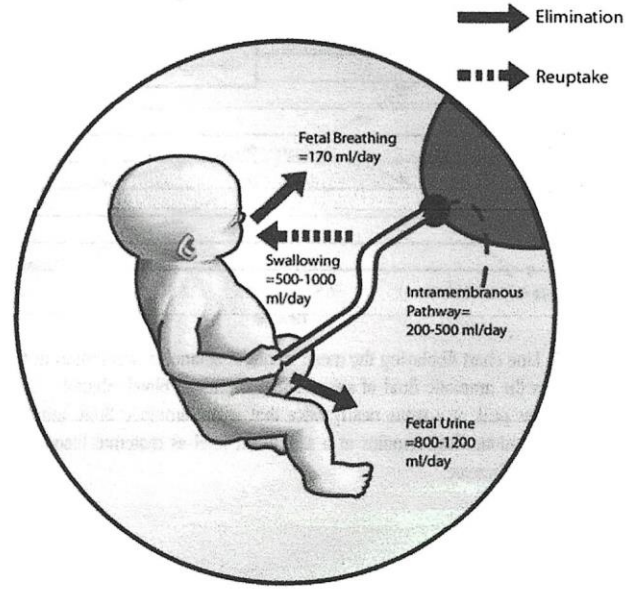


Figure 4 Pathways of amniotic fluid recirculation.[27] Production and reuptake are usually near equilibrium and therefore alcohol elimination through these pathways is highly ineffective.

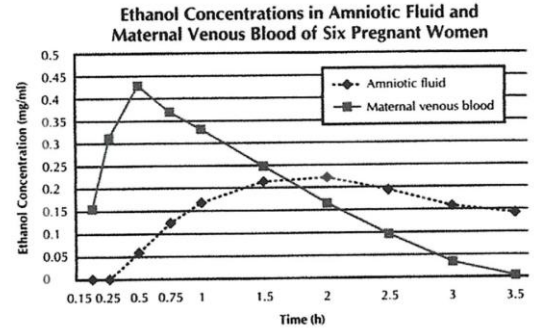
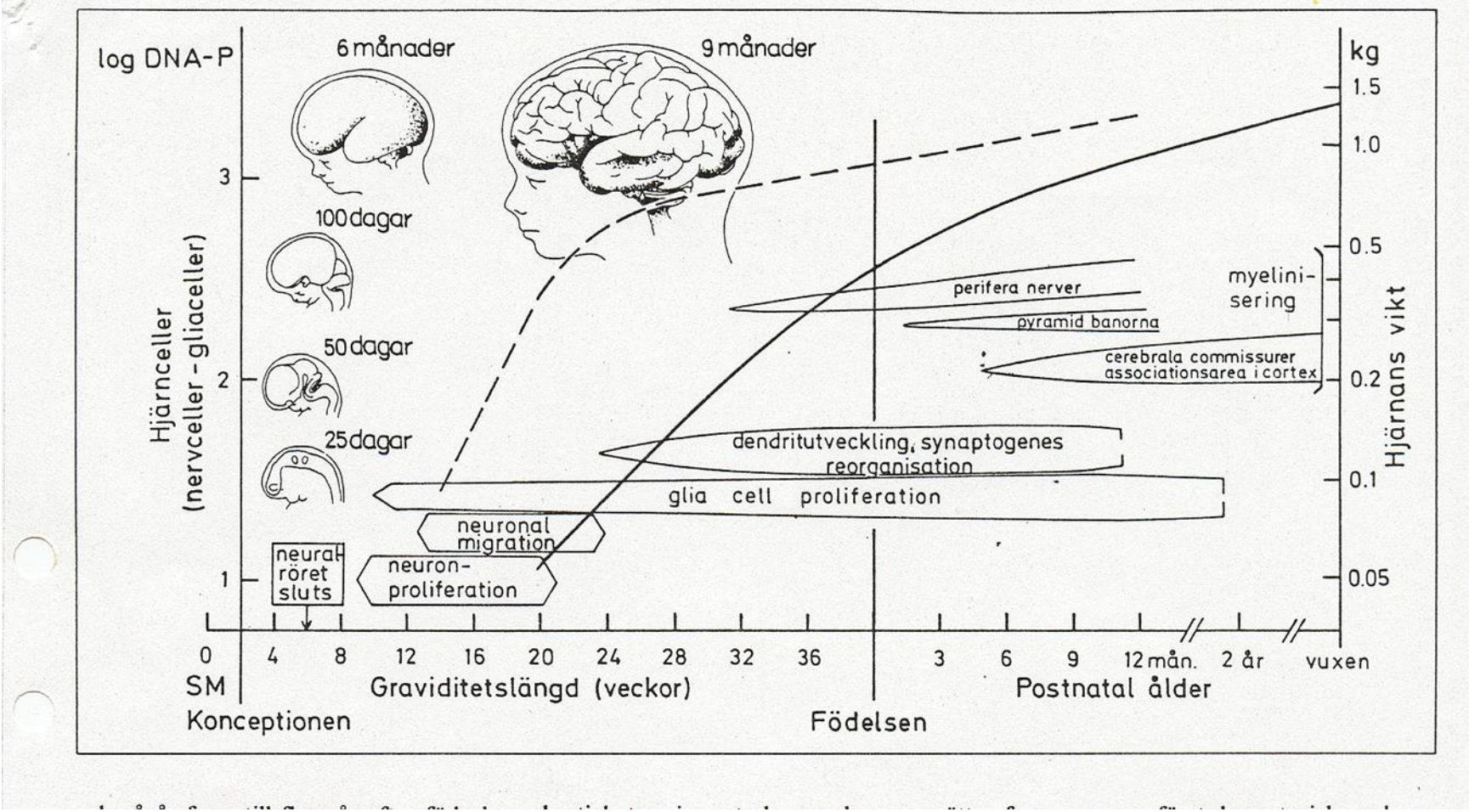


Figure 5 Line chart displaying the mean values of ethanol concentration in the blood versus the amniotic fluid of six pregnant women.[28] Blood ethanol concentrations peak at a value nearly twice that of the amniotic fluid. Ethanol within the amniotic fluid remains at a significant level as maternal blood concentrations decrease.

Embryo och fosterutvecklingen

Hugo Lagercrantz, 1985 Läkartidningen



Alkoholrelaterade missbildningar

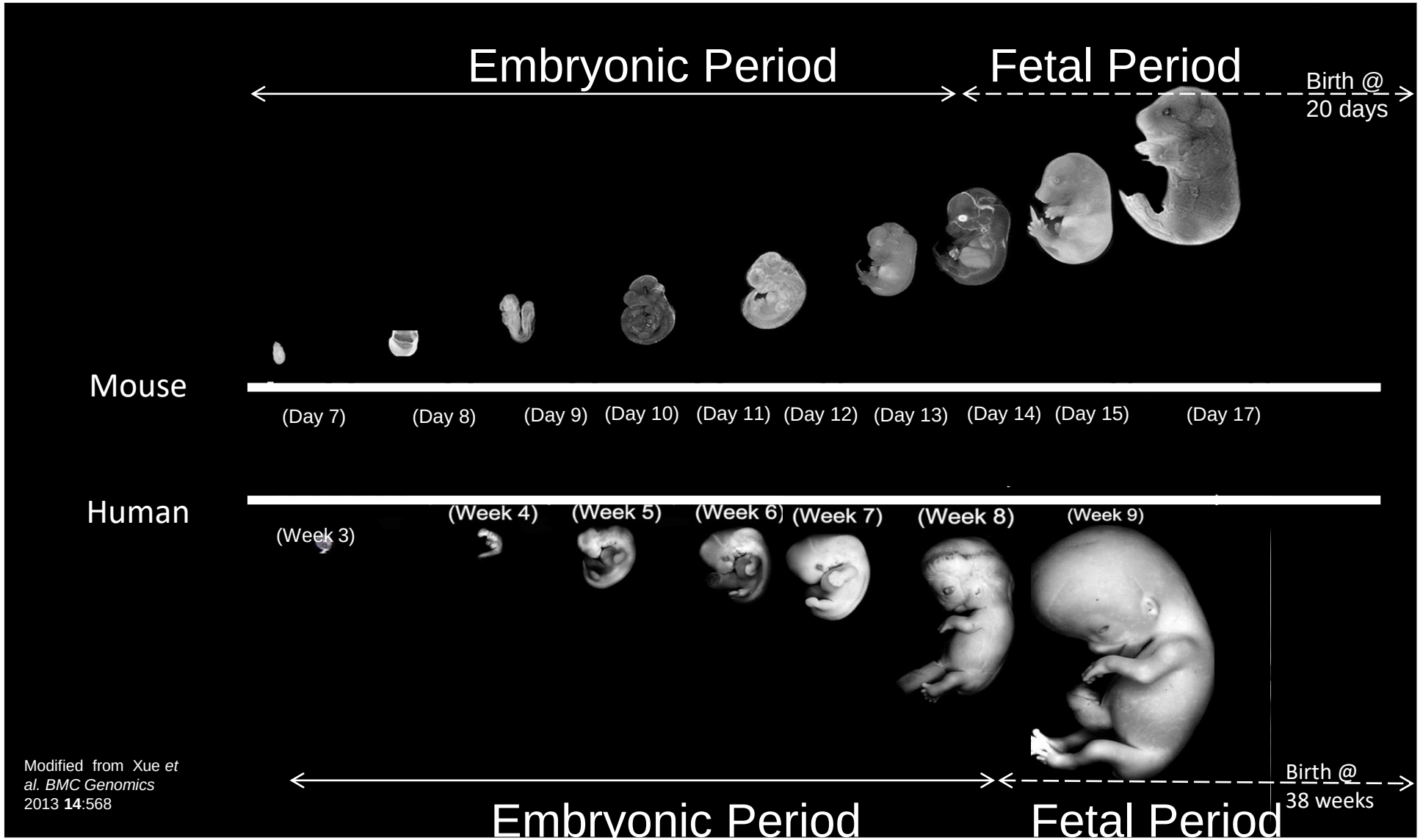
- **CNS**
- VOC
- skelett (radio-ulnar syntostos, kotanomalier, kontrakturer …)
- ögonmissbildningar
- hörselnedsättningar
- njurmissbildningar
- …

I. Neurobehavioral Outcome of Prenatal Exposure in Humans or Animals

Adapted from Envioronmental Health Perspectives Supplement 3 june 2000

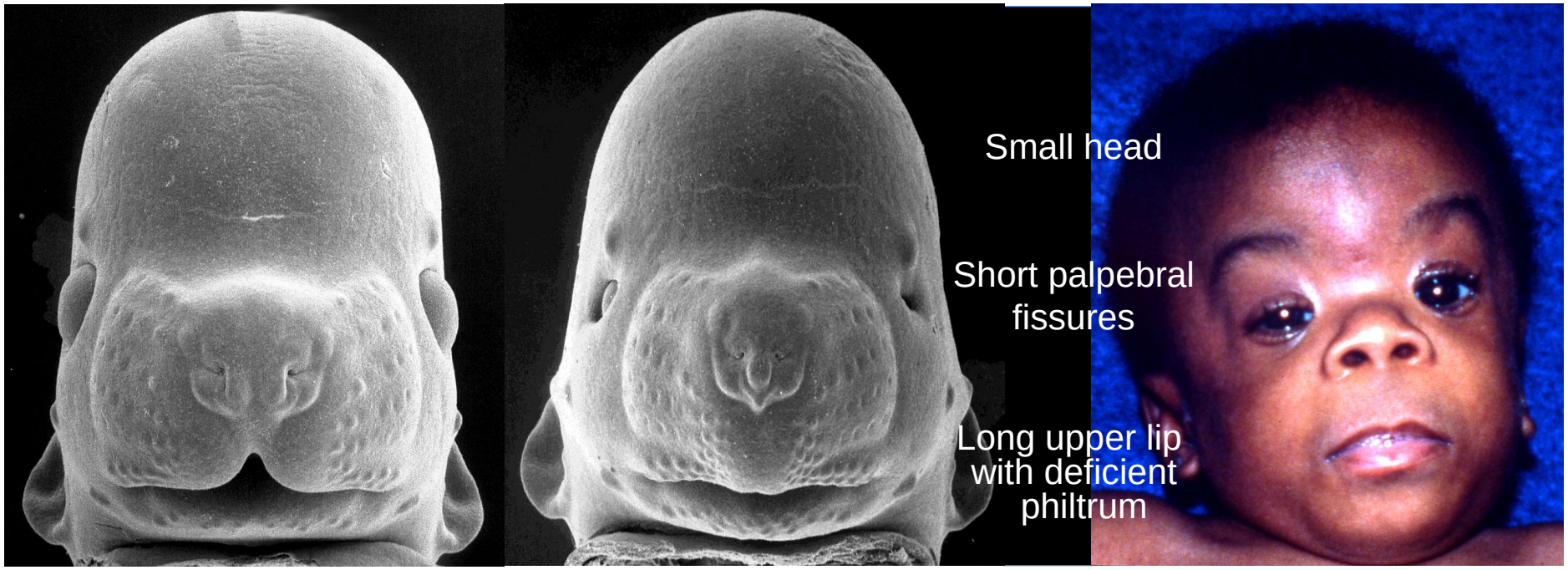
	Alkohol	Metyl Hg	Strålning	Phenytoin	PCB	Opioider	Marijuan	Tobak	Bly
Hjärnmissbildning	+ NDR	+DR	+DR	-	-	NE	NE	NE	NE
Utvecklingsstörning	+DR	+DR	+DR	NE	?	NE	NE	NE	NE
Kognitiv dysfunktion	+DR	+DR	+DR	+DR	+DR	NE	?	+DR	+DR
HD (Hyperactivity)	+DR	-	-	-	+DR	NE	NE	+DR	?
ADD (Attentio DD)	+DR	-	-	-	-	?	+NDR	+NDR	?
Gångstörning	+DR	+DR	+DR	-	+DR	NE	+NDR	NE	NE
DCD	+DR	-	-	-	NE	?	NE	NE	?
MPD	+DR	+DR	+DR	-	+DR	NE	NE	+DR	+NDR
Neo Abstinens	+NDR	-	-	-	-	+DR	?	+DR	-

Mouse and Human Development are very Similar



Bilder återgiven med tillstånd av Kathleen K. Sulik, PhD

Dysmorfologi vid FAS musmodell



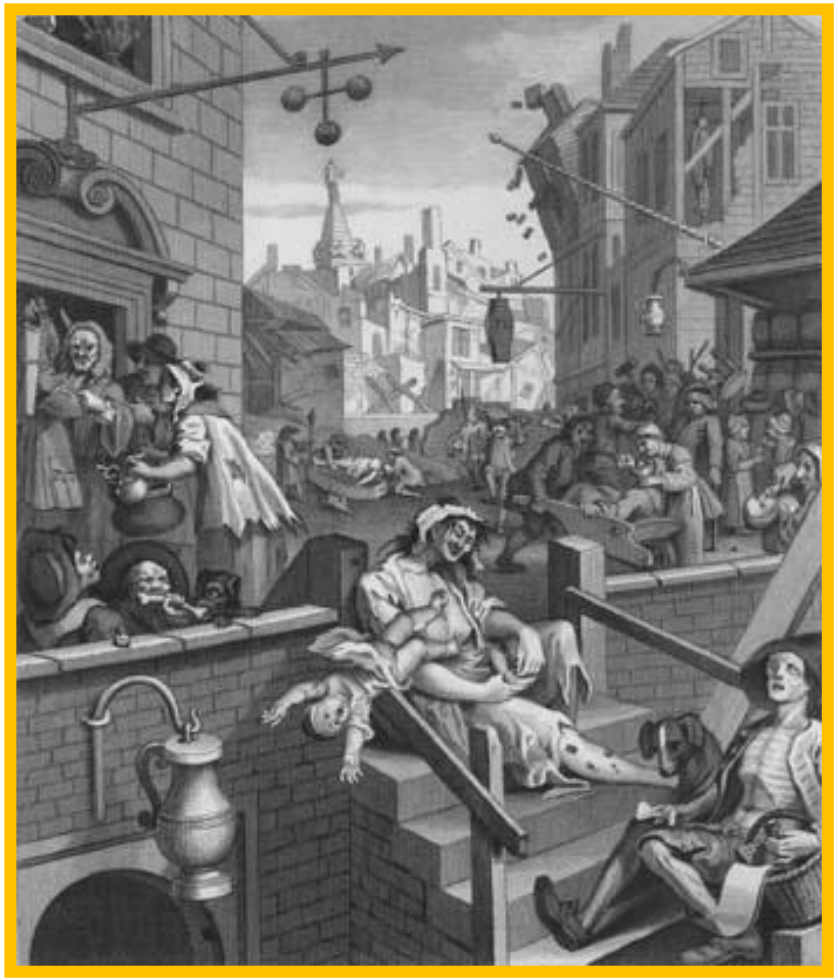
Normal mouse fetus

Alcohol-exposed mouse fetus

Child with FAS

Bilder återgiven med tillstånd av Kathleen K. Sulik, PhD

alkohol som känd skadeverkare



“Gin Lane” av William Hogarth (1697-1764)

*Tidiga observationer med teratologisk bäring, men kunskapen **glöms**…*

- London College of physicians 1725
- Sullivan 1899 600 barn till alkoholister jmf 28
- Ballantyne 1904 noterar missbildningar, spontan aborter och prematuritet
- Sullivan 1906
- Förbudstiden
- Efter förbudstiden förkastades den tidigare kunskapen av läkare som Jellinek m fl 1940. 1942 och Keller 1955
- Alkoholdropp vid prematurt värkarbete Fuchs et al 1967

Alkoholfetopati återupptäcks ”fokuserad uppmärksamhet”

- Lemoine 1964-68 N=127
- 1973 Smith and Jones N=8
- 1978 Olegård m fl

Hur vanligt är FAS/FASS – senaste 10 åren:

Abel och Sokol 1987, 1991	FAS allmän befolkning 0,33-2,2/1000 1/250 vissa minoriteter
Olegård et al 1979	FAS 1,7/1000 ’ FAE 1,7/1000 och komb.1/300
Sampson et al 1997 USA May et al 2006 Italien <u>Subpopulationer</u> May et al 2002 Sydafrika Riely et al 2003 Moskva	FAS/FAE 9,1/1000 FASD 2-4.5% FAS+PFAS 6,8-8,9% FAS 79/1000

epidemiologi

FASD-prevalens

”in school study” 7 åringar i USA 1,1-5%

Adoptivbarn från Österuropa VGR f 1990-95 50%

Olegård et al 1979 1/300

Svensk i skolan undersökning?

- Exponering?
- Typ av exponering?
- Individuella förutsättningar?
  - Mängd
  - Max konc
  - Andra samtidiga droger
  - Timingiembryogenes - fetalperiod
- Studerad population?
- Representativitet?

May, P. A., Chambers, C. D., Kalberg, W. et al (2018). Prevalence of fetal alcohol spectrum disorders in 4 US communities. *Jama*, *319*(5), 474-482.

JAMA | Original Investigation

Prevalence of Fetal Alcohol Spectrum Disorders in 4 US Communities

Philip A. May, PhD; Christina D. Chambers, PhD, MPH; Wendy O. Kalberg, MA; Jennifer Zellner, PhD; Haruna Feldman, PhD; David Buckley, MA; David Kopald; Julie M. Hasken, MPH; Ronghui Xu, PhD; Gordon Honerkamp-Smith, MS; Howard Taras, MD; Melanie A. Manning, MD; Luther K. Robinson, MD; Margaret P. Adam, MD; Omar Abdul-Rahman, MD; Keith Vaux, MD; Tamison Jewett, MD; Amy J. Elliott, PhD; Julie A. Kable, PhD; Natachi Akshoomoff, PhD; Daniel Falk, PhD; Judith A. Arroyo, PhD; Dale Hereld, MD, PhD; Edward P. Riley, PhD; Michael E. Charness, MD; Claire D. Coles, PhD; Kenneth R. Warren, PhD; Kenneth Lyons Jones, MD; H. Eugene Hoyme, MD

Editorial page 448
Supplemental content
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IMPORTANCE Fetal alcohol spectrum disorders are costly, life-long disabilities. Older data suggested the prevalence of the disorder in the United States was 10 per 1000 children; however, there are few current estimates based on larger, diverse US population samples.

OBJECTIVE To estimate the prevalence of fetal alcohol spectrum disorders, including fetal alcohol syndrome, partial fetal alcohol syndrome, and alcohol-related neurodevelopmental disorder, in 4 regions of the United States.

DESIGN, SETTING, AND PARTICIPANTS Active case ascertainment methods using a cross-sectional design were used to assess children for fetal alcohol spectrum disorders between 2010 and 2016. Children were systematically assessed in the 4 domains that contribute to the fetal alcohol spectrum disorder continuum: dysmorphic features, physical growth, neurobehavioral development, and prenatal alcohol exposure. The settings were 4 communities in the Rocky Mountain, Midwestern, Southeastern, and Pacific Southwestern regions of the United States. First-grade children and their parents or guardians were enrolled.

EXPOSURES Alcohol consumption during pregnancy.

MAIN OUTCOMES AND MEASURES Prevalence of fetal alcohol spectrum disorders in the 4 communities was the main outcome. Conservative estimates for the prevalence of the disorder and 95% CIs were calculated using the eligible first-grade population as the denominator. Weighted prevalences and 95% CIs were also estimated, accounting for the sampling schemes and using data restricted to children who received a full evaluation.

RESULTS A total of 6639 children were selected for participation from a population of 13 146 first-graders (boys, 51.9%; mean age, 6.7 years [SD, 0.41] and white maternal race, 79.3%). A total of 222 cases of fetal alcohol spectrum disorders were identified. The conservative prevalence estimates for fetal alcohol spectrum disorders ranged from 11.3 (95% CI, 7.8-15.8) to 50.0 (95% CI, 39.9-61.7) per 1000 children. The weighted prevalence estimates for fetal alcohol spectrum disorders ranged from 31.1 (95% CI, 16.1-54.0) to 98.5 (95% CI, 57.5-139.5) per 1000 children.

CONCLUSIONS AND RELEVANCE Estimated prevalence of fetal alcohol spectrum disorders among first-graders in 4 US communities ranged from 1.1% to 5.0% using a conservative approach. These findings may represent more accurate US prevalence estimates than previous studies but may not be generalizable to all communities.

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epidemiologi

JAMA Pediatrics | Original Investigation

Global Prevalence of Fetal Alcohol Spectrum Disorder Among Children and Youth

A Systematic Review and Meta-analysis

Shannon Lange, MPH; Charlotte Probst, MSc; Gerrit Gmel, MSc; Jürgen Rehm, PhD; Larry Burd, PhD; Svetlana Popova, PhD

Editorial page 940
Supplemental content

IMPORTANCE Prevalence estimates are essential to effectively prioritize, plan, and deliver health care to high-needs populations such as children and youth with fetal alcohol spectrum disorder (FASD). However, most countries do not have population-level prevalence data for FASD.

OBJECTIVE To obtain prevalence estimates of FASD among children and youth in the general population by country, by World Health Organization (WHO) region, and globally.

DATA SOURCES MEDLINE, MEDLINE in process, EMBASE, Education Resource Information Center, Cumulative Index to Nursing and Allied Health Literature, Web of Science, PsychINFO, and Scopus were systematically searched for studies published from November 1, 1973, through June 30, 2015, without geographic or language restrictions.

STUDY SELECTION Original quantitative studies that reported the prevalence of FASD among children and youth in the general population, used active case ascertainment or clinic-based methods, and specified the diagnostic guideline or case definition used were included.

DATA EXTRACTION AND SYNTHESIS Individual study characteristics and prevalence of FASD were extracted. Country-specific random-effects meta-analyses were conducted. For countries with 1 or no empirical study on the prevalence of FASD, this indicator was estimated based on the proportion of women who consumed alcohol during pregnancy per 1 case of FASD. Finally, WHO regional and global mean prevalence of FASD weighted by the number of live births in each country was estimated.

MAIN OUTCOMES AND MEASURES Prevalence of FASD.

RESULTS A total of 24 unique studies including 1416 unique children and youth diagnosed with FASD (age range, 0-16.4 years) were retained for data extraction. The global prevalence of FASD among children and youth in the general population was estimated to be 7.7 per 1000 population (95% CI, 4.9-11.7 per 1000 population). The WHO European Region had the highest prevalence (19.8 per 1000 population; 95% CI, 14.1-28.0 per 1000 population), and the WHO Eastern Mediterranean Region had the lowest (0.1 per 1000 population; 95% CI, 0.1-0.5 per 1000 population). Of 187 countries, South Africa was estimated to have the highest prevalence of FASD at 111.1 per 1000 population (95% CI, 71.1-158.4 per 1000 population), followed by Croatia at 53.3 per 1000 population (95% CI, 30.9-81.2 per 1000 population) and Ireland at 47.5 per 1000 population (95% CI, 28.0-73.6 per 1000 population).

CONCLUSIONS AND RELEVANCE Globally, FASD is a prevalent alcohol-related developmental disability that is largely preventable. The findings highlight the need to establish a universal public health message about the potential harm of prenatal alcohol exposure and a routine screening protocol. Brief interventions should be provided, where appropriate.

Author Affiliations: Author affiliations are listed at the end of this article.

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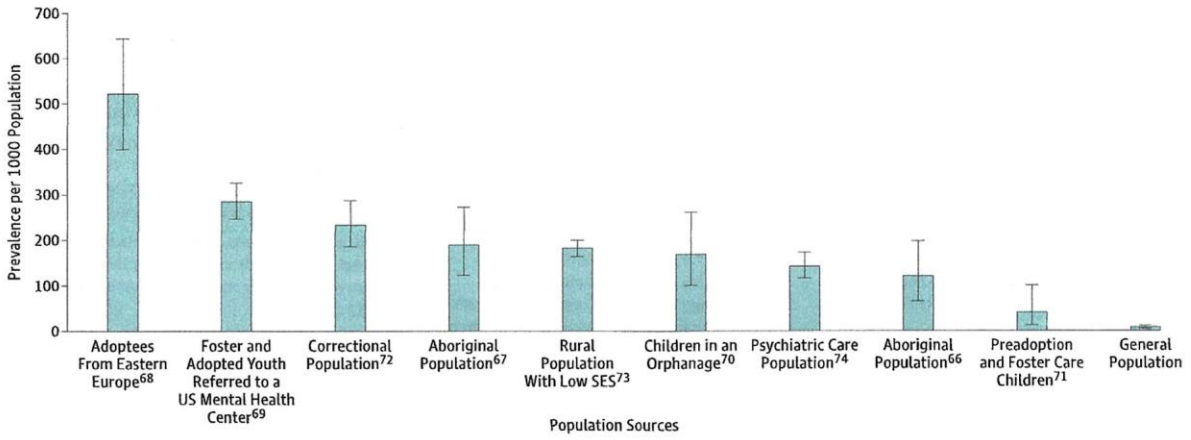
Published online August 21, 2017.

Figure 2. Comparison of the Prevalence of Fetal Alcohol Spectrum Disorder in Special Populations With the Global Prevalence Among Children and Youth in the General Population



Data in special populations are obtained from select studies. Special populations include adoptees from Eastern Europe in Sweden (521.1 per 1000 population; Landgren et al[68]), foster and adopted youth referred to a US children's mental health center (285.2 per 1000 population; Chasnoff et al[69]), a correctional population in Canada (233.5 per 1000 population; Fast et al[72]), an aboriginal population in Canada (189.7 per 1000 population; Robinson et al[67]), a rural population with low socioeconomic status (SES) in South Africa (182.4 per 1000 population; de Vries et al[73]), children in an orphanage in Brazil (170.2 per 1000 population; Strömland et al[70]), a US population in psychiatric care (142.4 per 1000 population; Bell and Chimata[74]), an aboriginal population in Australia (120.4 per 1000 population; Fitzpatrick et al[66]), and children before adoption or in foster care in Israel (40.0 per 1000 population; Tenenbaum et al[71]). Prevalence in the general population is described in Table 2. Error bars indicate 95% CI.

Konsekvenser av högre FASD-prevalens än förväntat – Op Ed JAMA 2018

Opinion

EDITORIAL

Implications of Higher Than Expected Prevalence of Fetal Alcohol Spectrum Disorders

Shannon Lange, MPH; Jürgen Rehm, PhD; Svetlana Popova, PhD

Fetal alcohol spectrum disorders are a group of serious, chronic, systemic diseases that are caused by prenatal alcohol exposure and characterized by central nervous system damage and physical deficits that subsequently lead to a wide range of permanent and lifelong health consequences. Individuals exposed to alcohol prenatally are at greater risk of having comorbid conditions[1] and premature mortality[2] than individuals who have not been exposed to alcohol prenatally. The financial burden associated with fetal alcohol spectrum disorders is substantial, estimated to cost (Can) $1.8 billion to Canadian society in 2013.[3]

Related article page 474

In this issue of *JAMA*, May and colleagues[4] report new prevalence estimates among 13 146 children enrolled in first grade between 2010 and 2016 from 4 diverse communities in the Rocky Mountain, Midwestern, Southeastern, and Pacific Southwestern regions of the United States. This study reports the prevalence of fetal alcohol spectrum disorders to be between 1% to 5% (using a conservative approach to estimation) and 3% to 10% (using a less conservative approach). Although the different approaches reflect the uncertainty about the actual prevalence, these new estimates are up to 10 times higher than those previously reported using similar methods from 2 single-site studies,[5,6] and up to 5 times higher than a recent meta-analysis of 6 studies from the United States with a pooled prevalence of 2%.[7] The authors cautioned that their findings may not be generalizable to all US communities but also suggested that their estimates are likely more accurate than previously reported estimates for the United States.

In this study, May and colleagues[4] used active-case ascertainment, which is the most reliable approach for estimating the prevalence of fetal alcohol spectrum disorders. Active-case ascertainment has 3 primary advantages over other approaches, including the (local) representativeness of data obtained by assessing an entire community or population; a high likelihood of accurate diagnosis by clinical specialists; and elimination of self-selection biases, which are characteristic of passive surveillance or clinic-based methods.[8] Accordingly, this study[4] could prompt other countries to perform such active-case ascertainment studies to obtain their own prevalence data, both among the general population and among high-risk populations such as those in the child protection and criminal justice systems and Aboriginal and psychiatric populations, in which the prevalence is suspected to be much higher.[7] An example of such an endeavor is the project currently under way by the World Health Organization, with the support of the National Institute on Alcohol Abuse and Alcoholism, on the estimation of the prevalence of fetal alcohol spectrum disorders in several countries of Central and Eastern Europe, Africa, and Canada. (The WHO International Collaborative Research Project on Child Development and Prenatal Risk Factors With a Focus on Fetal Alcohol Spectrum Disorders is available by request from WHO Department of Mental Health and Substance Abuse, Management of Substance Abuse).

The finding of May and colleagues[4] that fetal alcohol spectrum disorders is not a rare condition among the general US population has substantial implications for clinicians and researchers, including that many cases are either missed or misdiagnosed; additional supports should be made available for affected children and adults; surveillance systems for affected children and for prenatal alcohol exposure are needed; and improved prevention efforts targeting prenatal alcohol use are clearly required.

Many cases of fetal alcohol spectrum disorders remain unrecognized or have been misdiagnosed.[9] In the study by May and colleagues, only 2 of 222 children had been previously diagnosed.[4] There are likely a number of contributing factors, such as unknown or unconfirmed prenatal alcohol exposure, overlapping diagnostic criteria with other neurodevelopmental disorders,[10] and high rates of comorbidity.[2] This problem is further exacerbated because there are a number of clinical diagnostic guidelines, and although the current criteria considerably overlap with one another, they lack diagnostic reliability due to low convergent validity.[11] Thus, a universal diagnostic approach needs to be accepted or developed.[12] Ideally, novel and reliable biomarkers for detecting fetal alcohol effects will be identified,[12] which could have significant implications for intervention and therapeutic services.

Many individuals with fetal alcohol spectrum disorders will require the support of different services and service systems throughout their lives, partly due to co-occurring secondary disabilities (eg, mental health problems, poor academic achievement and school failure, and involvement with the law).[13] As such, provision of appropriate diagnosis, interventions, and support services early in life and maintained throughout the life span is essential. Such supports and interventions can significantly improve an affected individual's quality of life and long-term prognosis.[14] Accurate prevalence estimates are crucial for effectively prioritizing, planning, and delivering the numerous required services.

The harmful effects of alcohol on a fetus result in many cases of preventable long-term disability and must be recognized globally as a public health problem. The prevalence

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Related article page 474

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Many cases of fetal alcohol spectrum disorders remain un-

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n=2033 32 skolor FASD: minst 2,4%-4,8%

Research

JAMA | Original Investigation

Prevalence of Fetal Alcohol Spectrum Disorders in 4 US Communities

Philip A. May, PhD; Christina D. Chambers, PhD, MPH; Wendy O. Kalberg, MA; Jennifer Zellner, PhD; Haruna Feldman, PhD; David Buckley, MA; David Kopald; Julie M. Hasken, MPH; Ronghui Xu, PhD; Gordon Honerkamp-Smith, MS; Howard Taras, MD; Melanie A. Manning, MD; Luther K. Robinson, MD; Margaret P. Adam, MD; Omar Abdul-Rahman, MD; Keith Vaux, MD; Tamison Jewett, MD; Amy J. Elliott, PhD; Julie A. Kable, PhD; Natacha Akshoomoff, PhD; Daniel Falk, PhD; Judith A. Arroyo, PhD; Dale Herald, MD, PhD; Edward P. Riley, PhD; Michael E. Charness, MD; Claire D. Coles, PhD; Kenneth R. Warren, PhD; Kenneth Lyons Jones, MD; H. Eugene Hoyme, MD

IMPORTANCE Fetal alcohol spectrum disorders are costly, life-long disabilities. Older data suggested the prevalence of the disorder in the United States was 10 per 1000 children; however, there are few current estimates based on larger, diverse US population samples.

OBJECTIVE To estimate the prevalence of fetal alcohol spectrum disorders, including fetal alcohol syndrome, partial fetal alcohol syndrome, and alcohol-related neurodevelopmental disorder, in 4 regions of the United States.

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Editorial page 448
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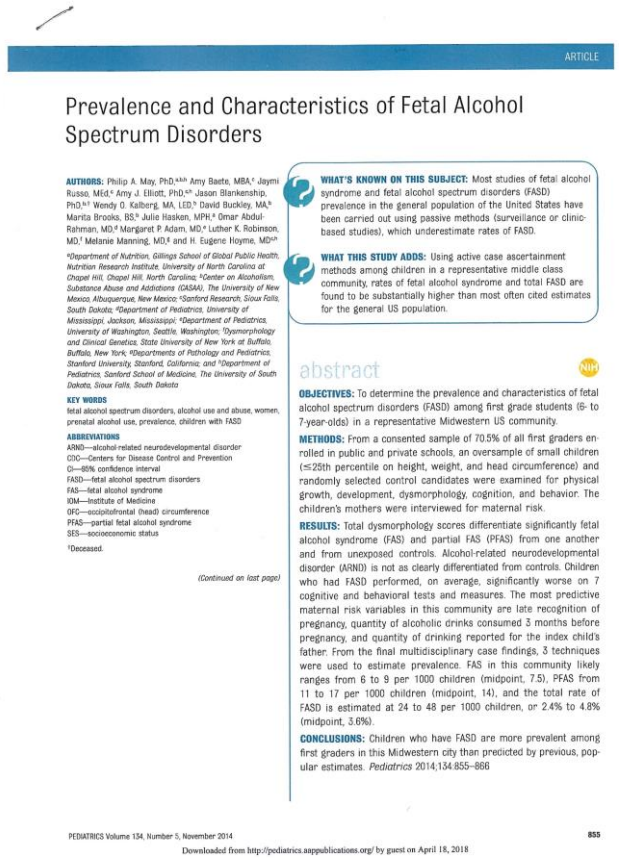

ARTICLE

Prevalence and Characteristics of Fetal Alcohol Spectrum Disorders

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KEY WORDS
fetal alcohol spectrum disorders, alcohol use and abuse, women, prenatal alcohol use, prevalence, children with FASD

ABBREVIATIONS
ARND—alcohol-related neurodevelopmental disorder
CDC—Centers for Disease Control and Prevention
CI—95% confidence interval
FASD—fetal alcohol spectrum disorders
FAS—fetal alcohol syndrome
IOM—Institute of Medicine
OFC—occipitofrontal (head) circumference
PFAS—partial fetal alcohol syndrome
SES—socioeconomic status

†Deceased.

(Continued on last page)

WHAT'S KNOWN ON THIS SUBJECT: Most studies of fetal alcohol syndrome and fetal alcohol spectrum disorders (FASD) prevalence in the general population of the United States have been carried out using passive methods (surveillance or clinic-based studies), which underestimate rates of FASD.

WHAT THIS STUDY ADDS: Using active case ascertainment methods among children in a representative middle class community, rates of fetal alcohol syndrome and total FASD are found to be substantially higher than most often cited estimates for the general US population.

abstract

OBJECTIVES: To determine the prevalence and characteristics of fetal alcohol spectrum disorders (FASD) among first grade students (6- to 7-year-olds) in a representative Midwestern US community.

METHODS: From a consented sample of 70.5% of all first graders enrolled in public and private schools, an oversample of small children (≤25th percentile on height, weight, and head circumference) and randomly selected control candidates were examined for physical growth, development, dysmorphology, cognition, and behavior. The children's mothers were interviewed for maternal risk.

RESULTS: Total dysmorphology scores differentiate significantly fetal alcohol syndrome (FAS) and partial FAS (PFAS) from one another and from unexposed controls. Alcohol-related neurodevelopmental disorder (ARND) is not as clearly differentiated from controls. Children who had FASD performed, on average, significantly worse on 7 cognitive and behavioral tests and measures. The most predictive maternal risk variables in this community are late recognition of pregnancy, quantity of alcoholic drinks consumed 3 months before pregnancy, and quantity of drinking reported for the index child's father. From the final multidisciplinary case findings, 3 techniques were used to estimate prevalence. FAS in this community likely ranges from 6 to 9 per 1000 children (midpoint, 7.5). PFAS from 11 to 17 per 1000 children (midpoint, 14), and the total rate of FASD is estimated at 24 to 48 per 1000 children, or 2.4% to 4.8% (midpoint, 3.6%).

CONCLUSIONS: Children who have FASD are more prevalent among first graders in this Midwestern city than predicted by previous, popular estimates. *Pediatrics* 2014;134:855–866

epidemiologi III Kanada BMC 2019
n=2555 students FASD 2% - 3%

Popova et al. BMC Public Health (2019) 19:845
https://doi.org/10.1186/s12889-019-7213-3

BMC Public Health

RESEARCH ARTICLE Open Access

Population-based prevalence of fetal alcohol spectrum disorder in Canada

Svetlana Popova[1,2,3,4*], Shannon Lange[1,4], Vladimir Poznyak[5], Albert E. Chudley[6], Kevin D. Shield[1,2], James N. Reynolds[7], Margaret Murray[8] and Jürgen Rehm[1,2,4,9,10]

Abstract

Background: Fetal alcohol spectrum disorder (FASD) is one of the most disabling potential outcomes of prenatal alcohol exposure. The population-based prevalence of FASD among the general population of Canada was unknown. The objective of this study was to determine the population-based prevalence of FASD among elementary school students, aged 7 to 9 years, in the Greater Toronto Area (GTA) in Ontario, Canada.

Methods: This screening study used a cross-sectional, observational design utilizing active case ascertainment, along with retrospective collection of prenatal alcohol exposure information. Data collection involved two phases. Phase I consisted of taking growth measurements, a dysmorphology examination, and obtaining a history of behavioral and/or learning problems. Phase II consisted of a neurodevelopmental assessment, maternal interview, and behavioral observations/ratings by parents/guardians. Final diagnostic screening conclusions were made by consensus by a team of experienced multidisciplinary experts during case conferences, using the 2005 Canadian guidelines for FASD diagnosis. The prevalence of FASD was estimated, taking into consideration the selection rate, which was used to account for students who dropped out or were lost to follow-up during each phase. Monte Carlo simulations were employed to derive the confidence interval (CI) for the point estimates.

Results: A total of 2555 students participated. A total of 21 cases of suspected FASD were identified. The prevalence of FASD was estimated to be 18.1 per 1000, or about 1.8%. Using a less conservative approach (sensitivity analysis), the prevalence of FASD was estimated to be 29.3 per 1000, or about 2.9%. Therefore, the population-based prevalence of FASD is likely to range between 2 and 3% among elementary school students in the GTA in Ontario, Canada.

Conclusions: This study provides the first population-based estimate of the prevalence of FASD in Canada. The estimate is approximately double or possibly even triple previous crude estimates. FASD prevalence exceeds that of other common birth defects such as Down's syndrome, spina bifida, trisomy 18, as well as autism spectrum disorder in Canada. More effective prevention strategies targeting alcohol use during pregnancy, surveillance of FASD, and timely interventions and support to individuals with FASD and their families are urgently needed.

Keywords: Fetal alcohol spectrum disorder, Fetal alcohol syndrome, Prevalence, Prenatal alcohol exposure, Canada

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- Tredubblar tidigare skattningar
- Överträffar andra vanliga medfödda tillstånd som Trisomi 21 och funktionsstörningar som F 84
- Bättre preventiva insatser krävs
- Fortlöpande bevakning av prevalens
- Tidig habilitering

Kliniska kriterier för diagnostisering av FASD

Updated Clinical Guidelines for Diagnosing Fetal Alcohol Spectrum Disorders

H. Eugene Hoyme, MD,[a,b] Wendy O. Kalberg, MA, LED,[a] Amy J. Elliott, PhD,[a] Jason Blankenship, PhD,[a,c] David Buckley, MA,[a] Anna-Susan Marais, B Cur Nursing,[d] Melanie A. Manning, MD,[a] Luther K. Robinson, MD,[a] Margaret P. Adam, MD,[a] Omar Abdul-Rahman, MD,[a] Tamison Jewett, MD,[a] Claire D. Coles, PhD,[e] Christina Chambers, PhD, MPH,[a] Kenneth L. Jones, MD,[a] Colleen M. Adnams, MBChB,[f] Prachi E. Shah, MD,[gh] Edward P. Riley, PhD,[h] Michael E. Charness, MD,[i] Kenneth R. Warren, PhD,[j] Philip A. May, PhD[a,k,l]

The adverse effects of prenatal alcohol exposure constitute a continuum of disabilities (fetal alcohol spectrum disorders [FASD]). In 1996, the Institute of Medicine established diagnostic categories delineating the spectrum but not specifying clinical criteria by which diagnoses could be assigned. In 2005, the authors published practical guidelines operationalizing the Institute of Medicine categories, allowing for standardization of FASD diagnoses in clinical settings. The purpose of the current report is to present updated diagnostic guidelines based on a thorough review of the literature and the authors' combined expertise based on the evaluation of >10 000 children for potential FASD in clinical settings and in epidemiologic studies in conjunction with National Institute on Alcohol Abuse and Alcoholism–funded studies, the Collaborative Initiative on Fetal Alcohol Spectrum Disorders, and the Collaboration on FASD Prevalence. The guidelines were formulated through conference calls and meetings held at National Institute on Alcohol Abuse and Alcoholism offices in Rockville, MD. Specific areas addressed include the following: precise definition of documented prenatal alcohol exposure; neurobehavioral criteria for diagnosis of fetal alcohol syndrome, partial fetal alcohol syndrome, and alcohol-related neurodevelopmental disorder; revised diagnostic criteria for alcohol-related birth defects; an updated comprehensive research dysmorphology scoring system; and a new lip/philtrum guide for the white population, incorporating a 45-degree view. The guidelines reflect consensus among a large and experienced cadre of FASD investigators in the fields of dysmorphology, epidemiology, neurology, psychology, developmental/behavioral pediatrics, and educational diagnostics. Their improved clarity and specificity will guide clinicians in accurate diagnosis of infants and children prenatally exposed to alcohol.

abstract

Disclaimer: The guidelines/recommendations in this article are not American Academy of Pediatrics policy, and publication herein does not imply endorsement.

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The adverse effects of alcohol on the developing fetus were described independently by Lemoine et al in 1968[1] and by Jones et al in 1973.[2] As with most malformation syndromes, the most severely affected children were described first, with the associated pattern of malformation termed fetal alcohol syndrome (FAS).[2] As pediatricians became more familiar with the clinical presentation of children prenatally exposed to alcohol, it became clear that the associated disabilities represent a spectrum, from mild to severe (fetal alcohol spectrum disorders or FASD). In 1996, the Institute of

SPECIAL ARTICLE

TABLE 1 Updated Criteria for the Diagnosis of FASD

Diagnostic Categories

(See Table 2 for definition of documented prenatal alcohol exposure)
I. FAS
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A diagnosis of FAS requires all features, A–D:
A. A characteristic pattern of minor facial anomalies, including ≥2 of the following:
1. Short palpebral fissures (≤10th centile)
2. Thin vermilion border of the upper lip (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
3. Smooth philtrum (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
B. Prenatal and/or postnatal growth deficiency
1. Height and/or weight ≤10th centile (plotted on a racially or ethnically appropriate growth curve, if available)
C. Deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology, including ≥1 of the following:
1. Head circumference ≤10th percentile
2. Structural brain anomalies
3. Recurrent nonfebrile seizures (other causes of seizures having been ruled out)
D. Neurobehavioral impairment*
1. For children ≥3 y of age (a or b):
a. WITH COGNITIVE IMPAIRMENT:
—Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥1.5 SD below the mean)
OR
—Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment or visual-spatial impairment)
b. WITH BEHAVIORAL IMPAIRMENT WITHOUT COGNITIVE IMPAIRMENT:
—Evidence of behavioral deficit in at least 1 domain ≥1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control)
2. For children <3 y of age:
—Evidence of developmental delay ≥1.5 SD below the mean
II. PFAS
For children with documented prenatal alcohol exposure, a diagnosis of PFAS requires features A and B:
A. A characteristic pattern of minor facial anomalies, including ≥2 of the following:
1. Short palpebral fissures (≤10th centile)
2. Thin vermilion border of the upper lip (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
3. Smooth philtrum (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
B. Neurobehavioral impairment*
1. For children ≥3 y of age (a or b):
a. WITH COGNITIVE IMPAIRMENT:
—Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥1.5 SD below the mean)
OR
—Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment or visual-spatial impairment)
b. WITH BEHAVIORAL IMPAIRMENT WITHOUT COGNITIVE IMPAIRMENT:
—Evidence of behavioral deficit in at least 1 domain ≥1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control)
2. For children <3 y of age:
—Evidence of developmental delay ≥1.5 SD below the mean
For children without documented prenatal alcohol exposure, a diagnosis of PFAS requires all features, A–C:
A. A characteristic pattern of minor facial anomalies, including ≥2 of the following:
1. Short palpebral fissures (≤10th centile)
2. Thin vermilion border of the upper lip (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
3. Smooth philtrum (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
B. Growth deficiency or deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology
1. Height and/or weight ≤10th centile (plotted on a racially or ethnically appropriate growth curve, if available), or:
2. Deficient brain growth, abnormal morphogenesis or neurophysiology, including ≥1 of the following:
a. Head circumference <10th percentile
b. Structural brain anomalies
c. Recurrent nonfebrile seizures (other causes of seizures having been ruled out)
C. Neurobehavioral impairment*
1. For children ≥3 y of age (a or b):
a. WITH COGNITIVE IMPAIRMENT:
—Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥1.5 SD below the mean)
OR
—Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment, or visual-spatial impairment)

Diagnostisk algoritm och differentialdiagnoser

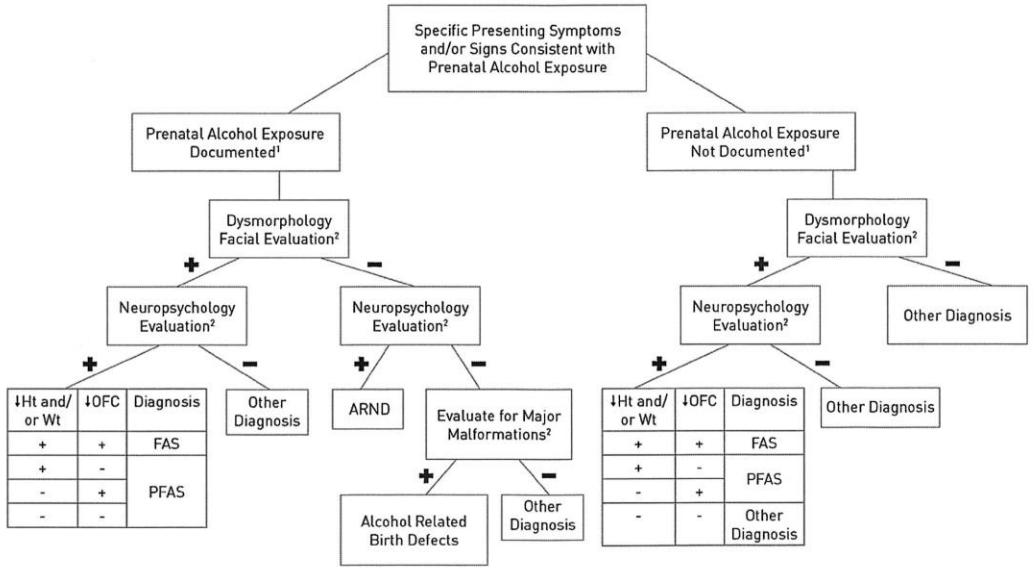


FIGURE 1
FASD diagnostic algorithm. See text for complete discussion. A positive dysmorphology facial evaluation requires 2 of the 3 cardinal facial features of FASD (short palpebral fissures, smooth philtrum, and this vermilion border of the upper lip). Cutoffs for neuropsychological testing are −1.5 SD. Cutoffs for stature, weight, and head circumference are at the 10th percentile.

TABLE 4 Genetic and Teratogenic Conditions to Be Considered in the Differential Diagnosis of FASD[79–81]

Malformation Syndrome	Etiology
Cornelia deLange Syndrome OMIM 122470	Autosomal dominant (Mutations in *NIPBL*, 60%)
Velocardiofacial Syndrome (del 22q11.2 Syndrome) OMIM #188400	Chromosome microdeletion (del 22q11.2)
Duplication 15q Syndrome OMIM 608636	Chromosome partial duplication (dup 15q)
Dubowitz Syndrome OMIM 223370	Autosomal recessive
Noonan Syndrome OMIM 163950	Autosomal dominant (Mutations in RAS-MAPK signal transduction pathway genes, *PTPN11*, *SOS1*, *KRAS*, *NRAS*, and others)
Williams Syndrome OMIM 194050	Chromosome microdeletion (del 7q11.23, a contiguous gene syndrome incorporating the elastin gene)
Fetal Hydantoin Syndrome	Teratogenic effects of hydantoin exposure during gestation
Fetal Valproate Syndrome	Teratogenic effects of valproic acid exposure during gestation
Maternal Phenlyketonuria Effects	Teratogenic effects of high levels of phenylalanine, accompanying poorly controlled maternal phenylketonuria
Toluene Embryopathy	Teratogenic effects of maternal solvent exposure during pregnancy

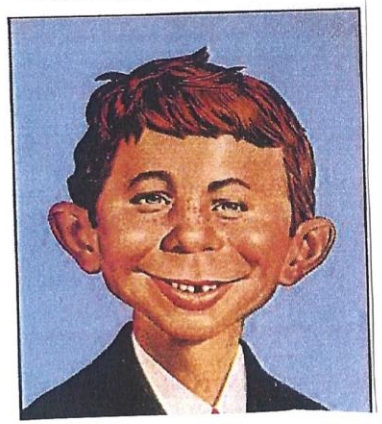
This list is not comprehensive. OMIM, Online Mendelian Inheritance in Man.[56]

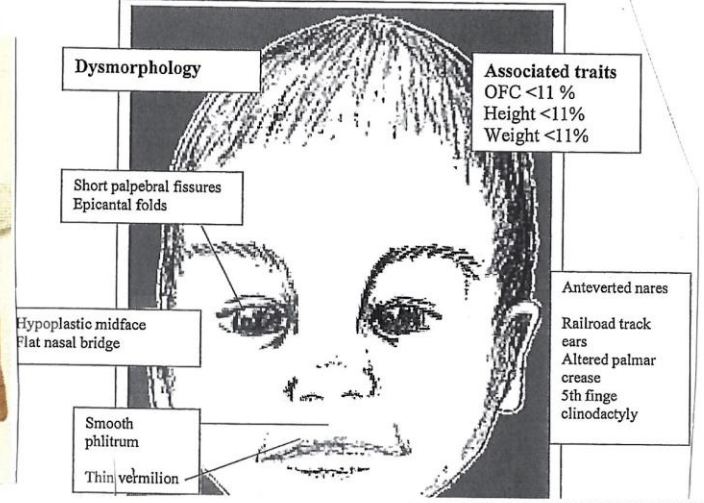
Funktionsnedsättningar associerade med FASD

TABLE 3 Developmental Emergence of Neurocognitive and Behavioral Deficits Associated With FASD

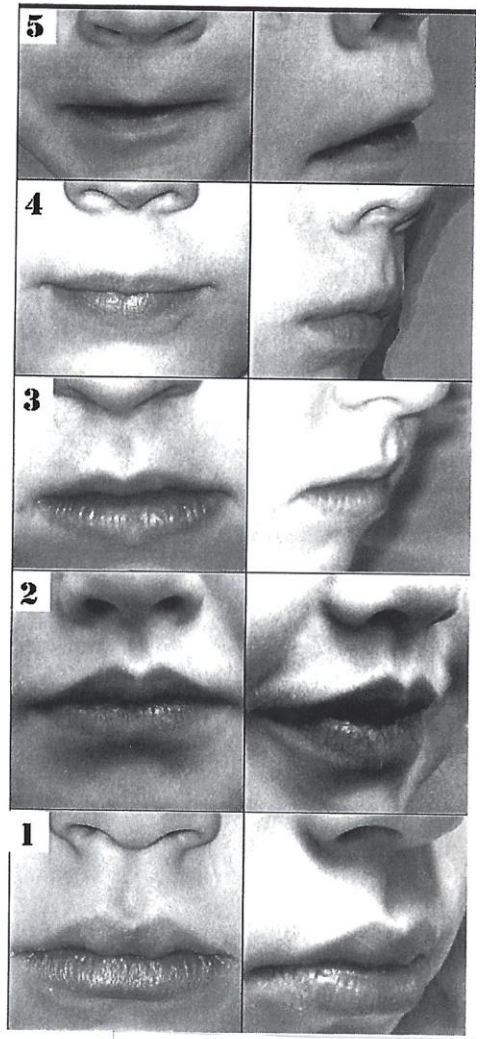
Areas of Brain Vulnerability in FASD	Neurocognitive/Behavioral Deficits Associated With Developmental Stage
Infancy: 0–2 y	
• Cortical synaptogenesis • Development of cortical gray matter • Myelination of sensory pathways • Maturation of the limbic system	Neurocognitive: • Delayed cognitive development or global developmental delay Self-Regulation: • Tremulousness, increased jitteriness • Difficulty with self-soothing, and being soothed • Emotional withdrawal, decreased infant affective functioning • Impaired stress reactivity; deficits in pain regulation • Less complex play
• Myelination of motor pathways	Adaptive: • Delayed gross and fine motor milestones • Poor feeding: poor sucking. Easily fatigued
Toddler/Preschool: 3–5 y	
Areas of Brain Vulnerability in FASD	Neurocognitive/Behavioral Deficits Associated With Developmental Stage
• Synaptogenesis • Development of cortical gray matter • Development of prefrontal cortex	Neurocognitive: • Delayed cognitive development or global developmental delay Self-Regulation: • Attention: difficulties with attention regulation; hyperactivity and impulsivity; difficulty shifting attention; impaired visual and auditory attention; difficulty with sustained attention • Executive function: difficulty encoding information; difficulty with multistep directions; difficulty with planning and organization; poor understanding of consequences • Sleep deficits: shortened sleep duration; increased sleep anxiety; parasomnias • Sensory processing: difficulty modulating sensory input; sensory seeking
• Development of temporal lobes	
• Development of dorsal motor cortex	Adaptive: • Delayed gross motor function: balance, coordination problems; "clumsiness" • Poor fine motor skills: difficulty with writing/drawing; poor dexterity; visual-spatial deficits; impaired visual-motor coordination
• Development of temporal lobes	• Delayed auditory processing: central auditory delay • Speech and language deficits: difficulties with language acquisition; receptive, expressive language delays; deficits in word processing/word recognition; articulation errors; deficits in social pragmatics • Memory deficits: difficulty remembering things previously learned
School-age: 6–12 y	
Areas of Brain Vulnerability in FASD	Neurocognitive/Behavioral Deficits Associated With Developmental Stage
• Decreased intracranial volume: • Decreased volume of parietal and temporal lobes • White matter abnormalities • Prefrontal cortex	Neurocognitive: • Lower intellectual quotient • Learning disabilities • Deficits in mathematics (numerical operations/global mathematics skills) Self-Regulation: • Executive function deficits: decreased working memory, decreased verbal fluency, poorer planning, sequencing, organization • Attention deficits: hyperactivity; impulsivity
• Temporal lobe	Adaptive: • Language: deficits in higher order language processing • Social pragmatics: deficits in social cognition: inappropriate social initiation/social interaction; inappropriate sexual behaviors • Memory: difficulty encoding/consolidating new memory
• Parietal lobe	• Language processing: impaired gestural communication; deficits in social perception • Visual-spatial: deficits in spatial processing; poor handwriting; impaired visual-motor integration
Adolescence: 13–21 y	
Areas of Brain Vulnerability in FASD	Neurocognitive/Behavioral Deficits Associated With Developmental Stage
• Decreased intracranial volume: • Decreased volume of parietal and temporal lobes • White matter abnormalities	Neurocognitive: • Lower intellectual quotient • Learning disabilities • Deficits in mathematics skills (numerical operations/global mathematics skills)

Alfred E Neuman (1894) 1956





North American White Lip/Philtrum Guide



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   3. Smooth philtrum (rank 4 or 5 on a racially normed lip/philtrum guide, if available)

B. Prenatal and/or postnatal growth deficiency
   1. Height and/or weight ≤10th centile (plotted on a racially or ethnically appropriate growth curve, if available)

C. Deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology, including ≥1 of the following:
   1. Head circumference ≤10th percentile
   2. Structural brain anomalies
   3. Recurrent nonfebrile seizures (other causes of seizures having been ruled out)

D. Neurobehavioral impairment[a]
   1. For children ≥3 y of age (a or b):
      a. WITH COGNITIVE IMPAIRMENT:

—Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥1.5 SD below the mean)

OR

—Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment or visual-spatial impairment)

      b. WITH BEHAVIORAL IMPAIRMENT WITHOUT COGNITIVE IMPAIRMENT:

—Evidence of behavioral deficit in at least 1 domain ≥1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control)

   2. For children <3 y of age:

—Evidence of developmental delay ≥1.5 SD below the mean

Differential diagnosis

(examples)

Cornelia de Lange Syndrome (OMIM#122470)

22q11.2 (OMIM#188400)

Noonan Syndrome (OMIM#163950) .....

FASD

I. FAS (+/- alcohol exposure)
II. PFAS
   a. Alcohol exp. A+D
   b. Non doc Alc. A+B+D
III. ARND Alcohol exp + D
IV. ARBD Alcohol exp + known alcohol related malformatior

Hoyme et al (2016) Updated Clinical guidelines for diagnosing

Pediatrics

Misdiagnosis and Missed Diagnoses

Misdiagnosis and Missed Diagnoses in Foster and Adopted Children With Prenatal Alcohol Exposure

Ira J. Chasnoff, MD, Anne M. Wells, PhD, Lauren King, MA

OBJECTIVE: The purpose of this article is to assess the rate of misdiagnosis and missed diagnoses of fetal alcohol spectrum disorders (FASD) among a population of foster and adopted youth referred to a children's mental health center.

METHODS: Data were collected from a sample of 547 children who underwent a comprehensive multidisciplinary diagnostic evaluation. Utilizing current diagnostic criteria, children were diagnosed, as appropriate, with fetal alcohol syndrome, partial fetal alcohol syndrome, alcohol-related neurodevelopmental disorder, or alcohol-related birth defects. Changes in rates of alcohol exposure-related diagnoses and cooccurring mental health disorders pre- and postassessment were analyzed by using McNemar's test for dependent proportions.

RESULTS: Among 156 children and adolescents who met criteria for a diagnosis within the fetal alcohol spectrum, 125 had never been diagnosed as affected by prenatal alcohol exposure, a missed diagnosis rate of 80.1%. Of the 31 who had been recognized before referral as affected by prenatal alcohol exposure, 10 children's FASD diagnoses were changed within the spectrum, representing a misdiagnosis rate of 6.4%. The remaining 21 (13.5%) children's diagnoses stayed the same. There also were significant changes in the rate of mental health diagnosis, and learning disorders, communication disorders, and intellectual disability, objective signs of neurocognitive damage, were not recognized in a significant number of children with FASD.

CONCLUSIONS: Within this clinical sample, 86.5% of youth with FASD had never been previously diagnosed or had been misdiagnosed. These high rates of missed diagnoses and misdiagnosis have significant implications for intervention and therapeutic services.

WHAT'S KNOWN ON THIS SUBJECT: Researchers speculate that children with fetal alcohol spectrum disorders often are not recognized or diagnosed correctly.

WHAT THIS STUDY ADDS: This is the first study to assess the rate of missed diagnoses and misdiagnosis in foster and adopted children with fetal alcohol spectrum disorders.

Children's Research Triangle, Chicago, Illinois

Dr Chasnoff served as principle investigator and lead author for this study; Dr Wells served as the data analyst for this study and participated directly in writing this article; and Ms King was responsible for data management and participated directly in writing this article.

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POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

- N=547
- 156 kunde diagnostiseras inom FASD
- 125 hade aldrig misstänkts varit exponerade under graviditet
- 80% var ”misssed”
- Jämför med May et al 2018 av c:a 200 FASD var två redan upptäckta

Biomarkörer för exponering

Brain Imaging and Behavior (2022) 16:69–77
https://doi.org/10.1007/s11682-021-00477-w

ORIGINAL RESEARCH

Combining neuroimaging and behavior to discriminate children with attention deficit-hyperactivity disorder with and without prenatal alcohol exposure

Joseph O'Neill[1] · Mary J. O'Connor[1] · Guldamla Kalender[1] · Ronald Ly[1] · Andrea Ng[1] · Andrea Dillon[1] · Katherine L. Narr[2] · Sandra K. Loo[1] · Jeffry R. Alger[2,3,4] · Jennifer G. Levitt[1]

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Abstract
In many patients, ostensible idiopathic attention deficit-hyperactivity disorder (ADHD) may actually stem from covert prenatal alcohol exposure (PAE), a treatment-relevant distinction. This study attempted a receiver-operator characteristic (ROC) classification of children with ADHD into those with PAE (ADHD+PAE) and those without (ADHD-PAE) using neurobehavioral instruments alongside magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) of supraventricular brain white matter. Neurobehavioral, MRS, and DTI endpoints had been suggested by prior findings. Participants included children aged 8–13 years, 23 with ADHD+PAE, 19 with familial ADHD-PAE, and 28 typically developing (TD) controls. With area-under-the-curve (AUC) >0.90, the Conners 3 Parent Rating Scale Inattention (CIn) and Hyperactivity/Impulsivity (CHp) scores and the Behavioral Regulation Index (BRI) of the Behavior Rating Inventory of Executive Function (BRIEF2) excellently distinguished the clinical groups from TD, but not from each other (AUC < 0.70). Combinations of MRS glutamate (Glu) and *N*-acetyl-compounds (NAA) and DTI mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), and fractional anisotropy (FA) yielded "good" (AUC > 0.80) discrimination. Neuroimaging combined with CIn and BRI achieved AUC 0.72 and AUC 0.84, respectively. But neuroimaging combined with CHp yielded 14 excellent combinations with AUC ≥ 0.90 (all $p < 0.0005$), the best being Glu·AD·RD·CHp/(NAA·FA) (AUC 0.92, sensitivity 1.00, specificity 0.82, $p < 0.0005$). Using Cho *in lieu* of Glu yielded AUC 0.83. White-matter microstructure and metabolism may assist efforts to discriminate ADHD etiologies and to detect PAE, beyond the ability of commonly used neurobehavioral measures alone.

Keywords Fetal alcohol spectrum disorder · Attention deficit hyperactivity disorder · Magnetic resonance spectroscopy · Diffusion tensor imaging · White matter

Introduction

Prenatal alcohol exposure (PAE) affects up to 5% of US children (May et al., 2018). ADHD is common in PAE (Mattson et al., 2019; O'Connor, 2014). Since, however, PAE often goes unrecognized, patients who have ADHD due to PAE (ADHD+PAE) are frequently misdiagnosed as having ADHD without PAE (ADHD-PAE) due to familial or other causes (Glass et al., 2014; Rasmussen, 2005; Wozniak et al., 2019). This has consequences as ADHD+PAE and ADHD-PAE may represent distinct subtypes of ADHD (Coles et al., 1997; Mattson et al., 2019). In particular, ADHD+PAE is less responsive to stimulants (Doig et al., 2008; O'Malley & Nanson, 2002; Peadon et al., 2009; Snyder et al., 1997). This is a major clinical issue. It is also a research issue. The

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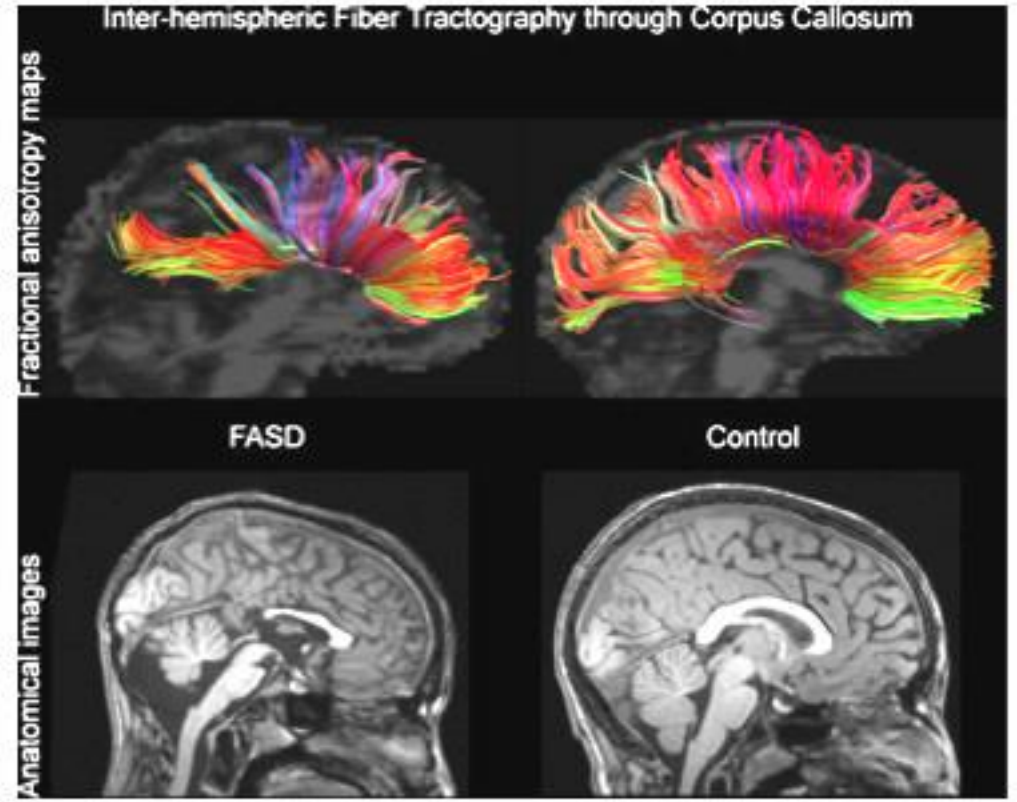

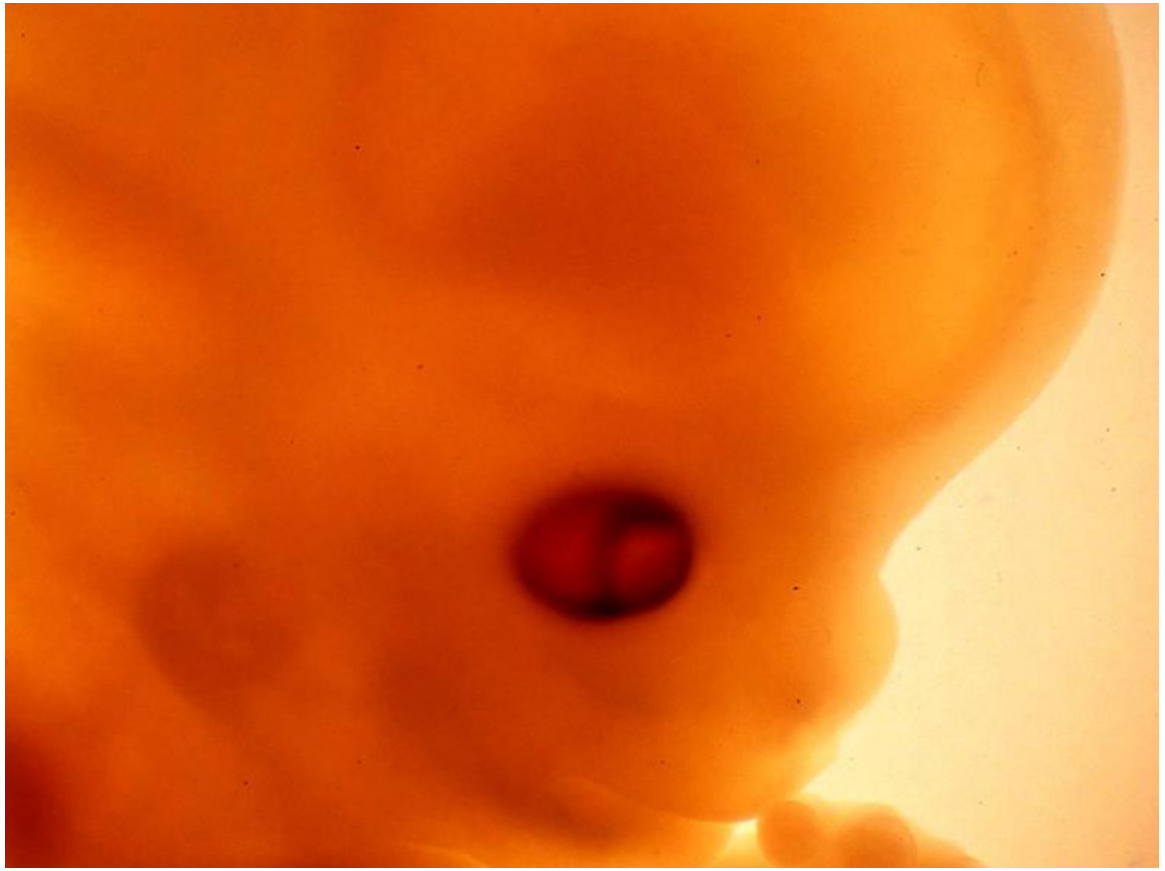

föräldrars = mammas = pappas = barnets intresse

…men det finns också andra intressen i samhället….pengar, politik …

”The World Health Organisation suggests that there is no safe level of drinking alcohol during pregnancy and that abstaining is the safest approach ”

Tack för uppmärksamheten