Early Identification and Prevention of Fetal Alcohol Spectrum Disorders: the NIAAA Collaborative Initiative in Eastern Europe

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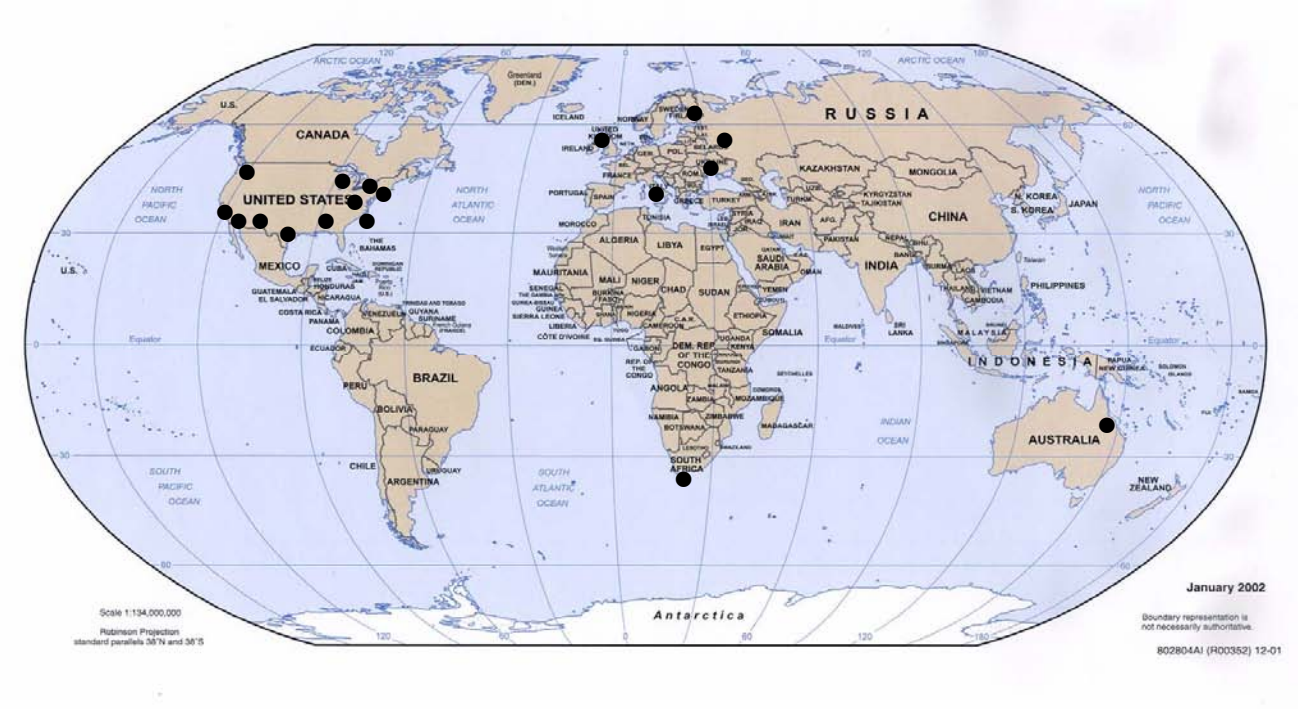
Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD)



CIFASD | Collaborative Initiative on Fetal Alcohol Spectrum Disorders

Latest News

- Pioneering researcher Dr. Kenneth Lyons Jones receives genetics award from March of Dimes
- Eye movement tasks can be used to assess fetal alcohol spectrum disorders
- Choline shows promise in reducing behavioral effects associated with prenatal alcohol exposure
- First-of-its-kind Italian school study finds high levels of prenatal alcohol exposure

Upcoming Events

07/17 - 07/23
Social Skills Development Series for 7 - 11 year old children affected by FASD

08/03 - 08/06
FASD Teen-Adult Conference Camp, Brainerd Minnesota

09/07
NineZero Conference (Nine months of Pregnancy, Zero Alcohol and Drugs) Sponsored by the Fetal Alcohol Spectrum Disorders Task Force of

Our Mission

The purpose of this consortium is to inform and develop effective interventions and treatment approaches for FASD, through multidisciplinary research involving basic, behavioral and clinical investigators and projects. We hope to develop an infrastructure to foster collaboration and coordinate basic, clinical and translational research on FASD. We welcome your input and your feedback.

National Institute on Alcohol Abuse and Alcoholism

Participating sites:

- San Diego State University
- Indiana University School of Medicine
- University of California, San Diego
- University of California, Los Angeles
- University of New Mexico
- Wayne State University
- Indiana University-Purdue University School of Science
- Ukrainian-American Birth Defects Program
- University of Washington
- Harvard University
- SUNY-Buffalo
- Folkhälsan Research Center-Helsinki
- University of Cape Town
- Moscow Institute of Psychiatry
- Moscow Institute of Obstetrics and Gynecology
- University of Rome

Under-recognition of FAS/D

- Difficulty in making the diagnosis, especially in the newborn period
- Lack of expertise among general pediatricians, or poor access to expert diagnostic teams to achieve consistent validity of diagnoses
- Lack of a clearly defined/distinct neurobehavioral phenotype
- Poor ascertainment of alcohol use by pregnant women

  - *Stoler JM et al J Pediatr 135:430-6 (1999)*
  - *Elliott EJ et al J Paediatr Child Health 42:698-703 (2006)*
  - *Elgen I et al Acta Pediatrica 96:237-41 (2007)*

Other unanswered questions

- How much alcohol, when and in what pattern presents a risk?
- What factors (e.g., genetic susceptibility, nutritional factors, other exposures) increase or decrease that risk for FASD, and can we intervene to prevent or ameliorate the disorder during pregnancy?
- What methods can be used to provide earlier identification of affected children in support of earlier intervention and treatment?

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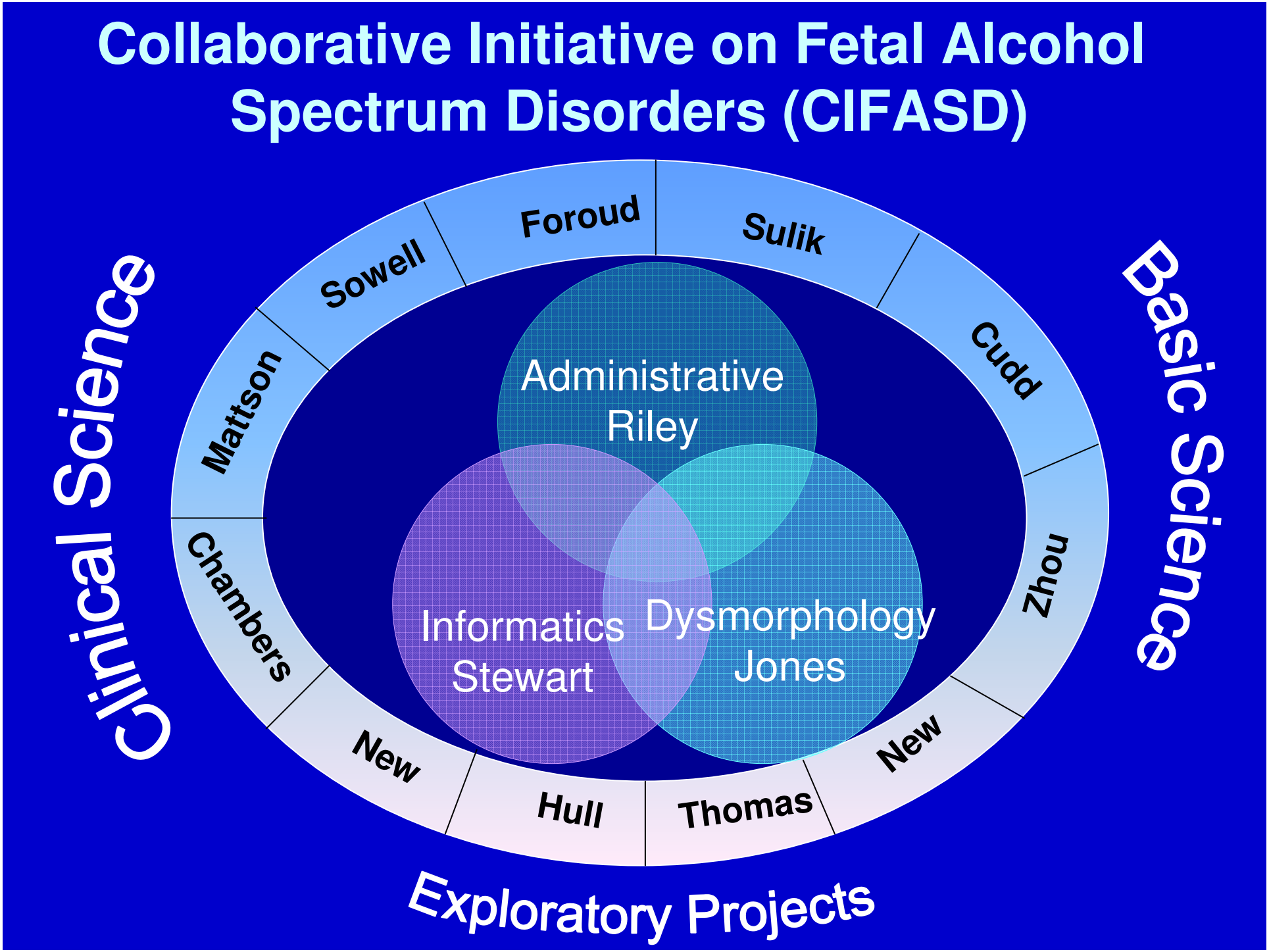
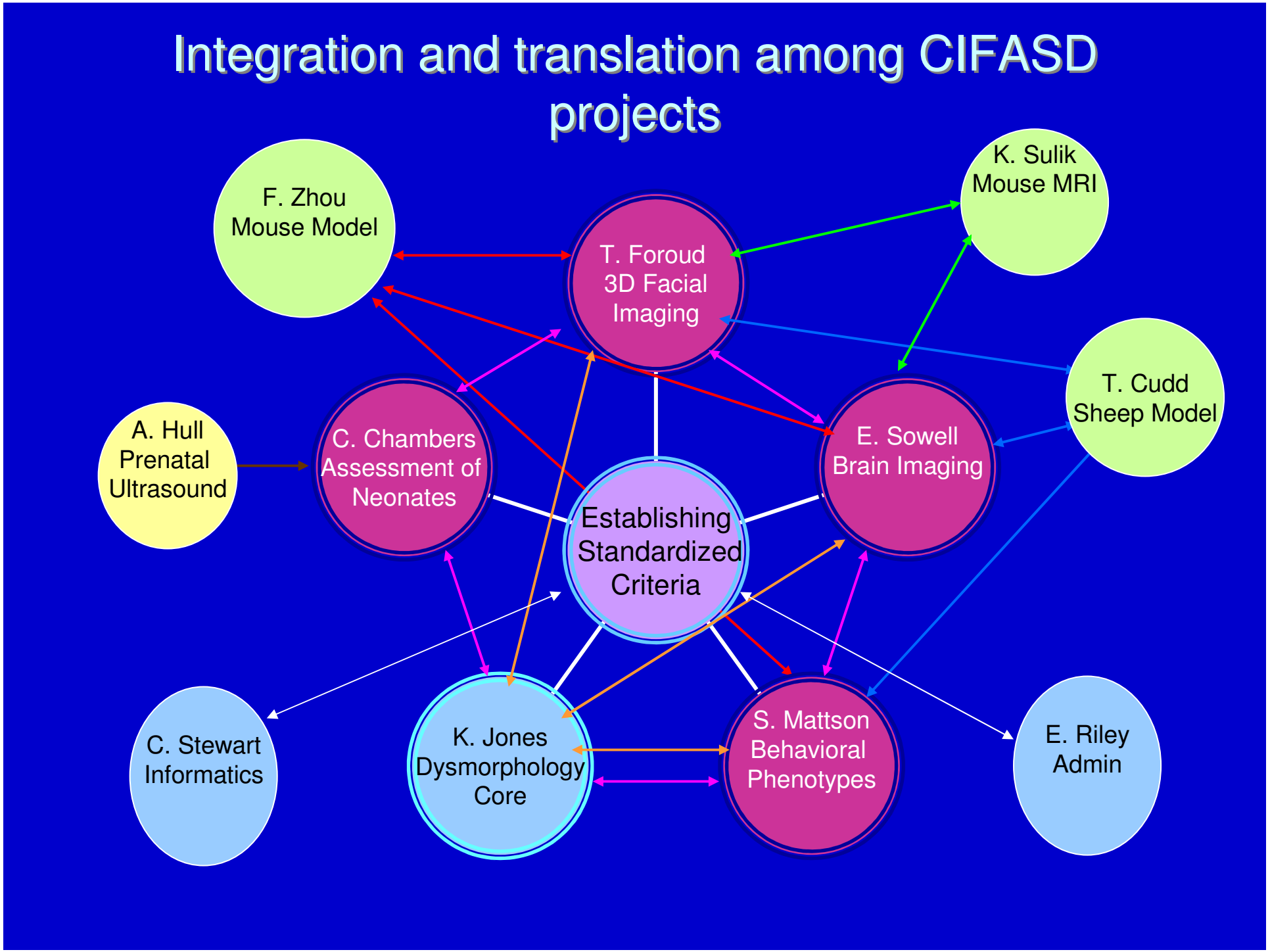
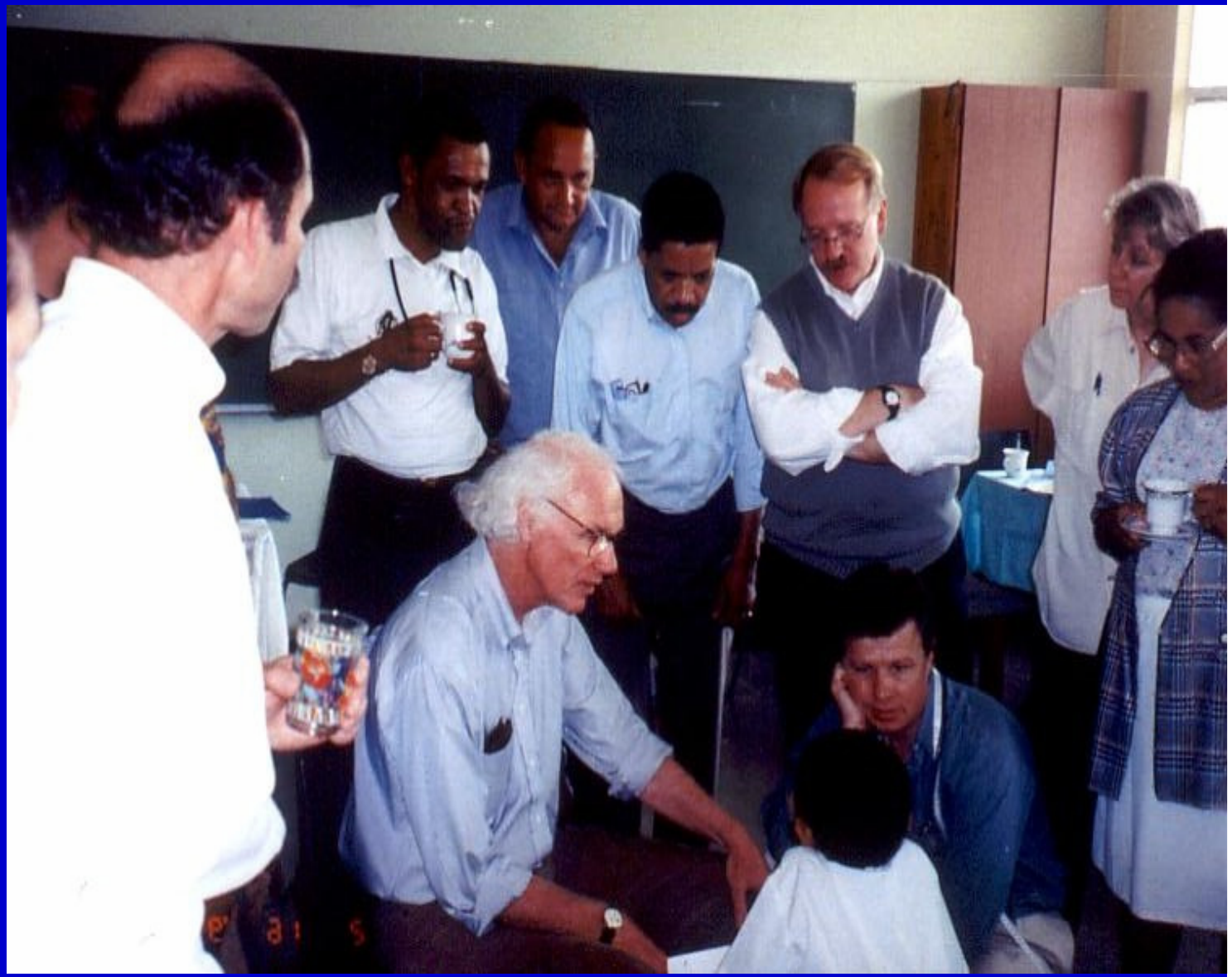


Integration and translation among CIFASD projects



South Africa

The diagnostic and research team in S.A., 1999



Prevalence of Fetal Alcohol Syndrome Western Cape Province, South Africa - Wave 3

Category	Number of Children
Total in 1st grade	1,013
Screened for growth (Tier 1)	818
Dysmorphology exam (Tier 2)	244 + 62
Preliminary diagnosis	30 FAS+78 Deferred
Final diagnosis	55 FAS+18 FASD
Rate	68.0 - 89.2/1,000

May PA et al Drug and Alcohol Dependence 88:259-71 (2007)

Italy


S.P.Q.S.
SCUOLA
ELEMENTARE
T.FALASCA
AC 370 HM

Prevalence of Fetal Alcohol Syndrome Lazio Province, Italy

Category	Number of Children
Total N in 1st grade	1,086
Total evaluated (Tier 1)	543
Total dysmorphology exam (Tier 2)	230
Final diagnosis	4 FAS + 17 FASD + 1 ARND
Rates	3.7 - 7.4 per 1,000 FAS 20.3 - 40.5 per 1,000 FASD

May PA Alcoholism Clin Exp Res 30:1562-75 (2006)

Russia

Fetal Alcohol Syndrome in Boarding Schools and Orphanages in Moscow

Facility	Total Number Children	Children Examined	Preliminary Diagnosis FAS	Confirmed Diagnosis FAS
Boarding Schools for Children Mental Deficiency N = 5	760	574 (76%)	35	27 (6.1%)
Orphanages for Children with Mental Deficiency N = 7	648	561 (87%)	71	69 (12.3%)
Orphanages for Normal or Mildly Delayed Children N = 3	218	190 (76%)	17	17 (8.9%)

Marintcheva G et al Soc Clin Psychiatry 3:17-22 (2003)

Russia/Ukraine CIFASD Clinical Project

- Prospective cohort study involving moderate to heavily exposed pregnant women screened during routine prenatal care and low/unexposed comparison women

Investigators/Collaborators

- Christina Chambers - UCSD
- Ken Jones - UCSD
- Claire Coles - Emory University
- Julie Kable - Emory University
- Carl Keen - UC Davis
- Jan Uriu-Adams - UC Davis
- Andrew Hull - UCSD
- Ludmila Bakhireva - UNM
- Lily Xu - UCSD
- Lyubov Yevtushok - Omni Net - Rivne, Ukraine
- Wladimir Wertelecki - U. So. Alabama
- Lela Kavteladze - Moscow Regional Institute of OB/Gyn
- Ludmila Joutchenko - Moscow Regional Genetics
- Anatoly Skalny - Center for Biotech Medicine, Moscow
- Pavel Ogurtsov -Friendship University, Moscow

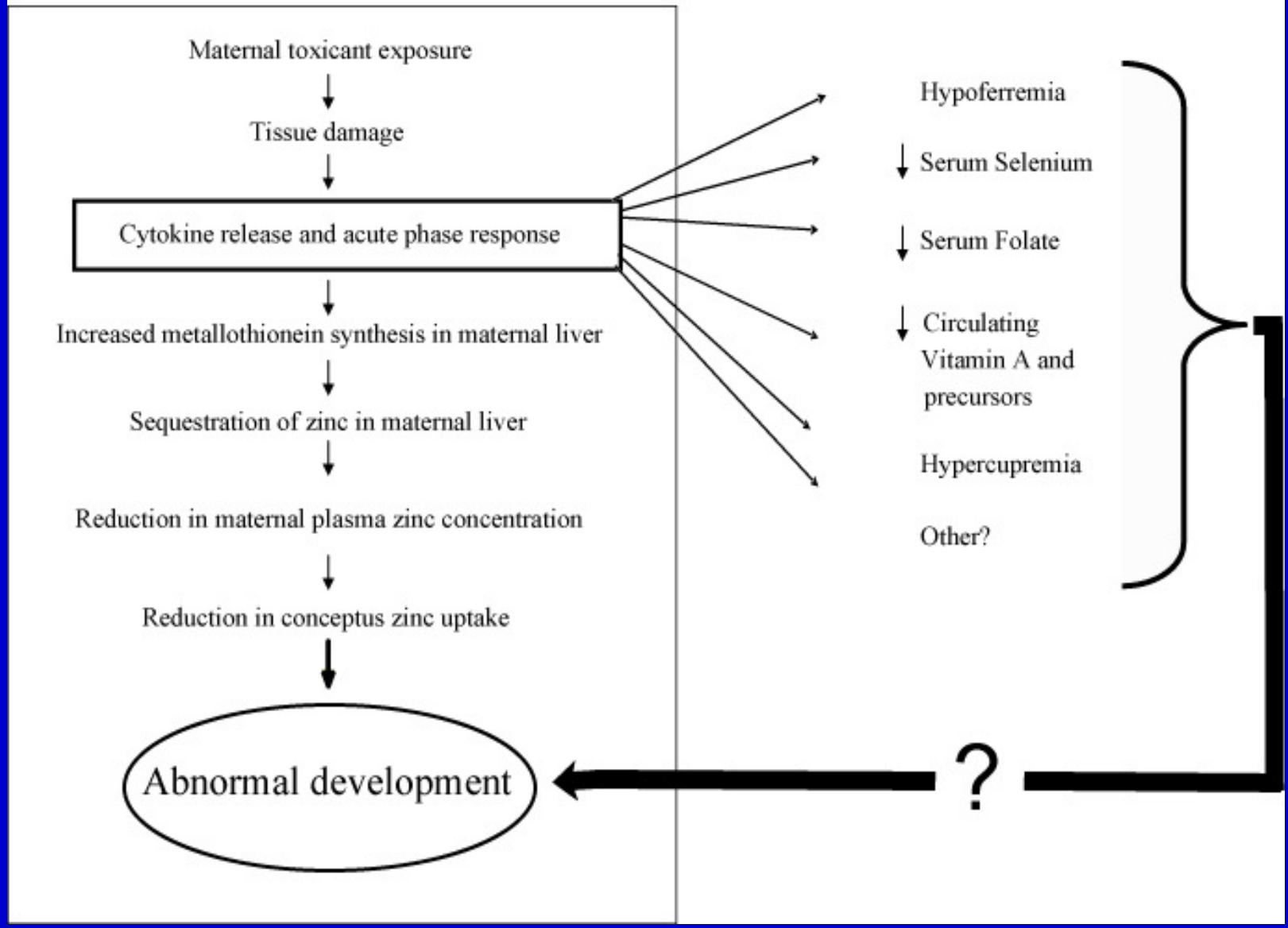
I. Spectrum of Outcomes

- To measure the birth prevalence and range of alcohol-related physical features and neurobehavioral impairment among children born to women who consume moderate to heavy amounts of alcohol in pregnancy relative to children born to mothers who report consuming low amounts or no alcohol during pregnancy
  - Three maternal interviews; biomarkers of exposure; banked DNA
  - Physical examinations by specially trained neonatologists/geneticists
  - Neurobehavioral testing at 6 m and 12 m

II. Nutrition

- To evaluate the contribution of specific micronutrients to risk for various features of FASD
- To conduct a randomized intervention trial of multivitamin supplementation with or without choline supplementation to reduce alcohol-related effects
    - Blood samples 2 times in pregnancy
    - Random assignment to multivitamin/mineral supplement
    - Random assignment to 700 mg choline supplement

Maternal Acute Phase Response and Nutrient Metabolism



FASD and choline

- Prenatal choline deficiency leads to long-lasting hippocampal dysfunction as well as memory and learning impairments

- In rats, perinatal choline supplementation attenuates the adverse effects of alcohol on hyperactivity and memory tasks

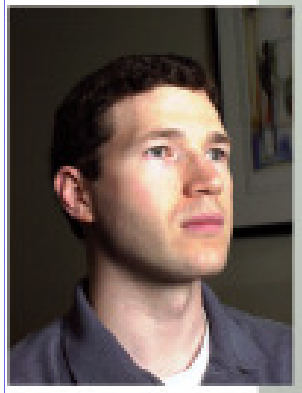
- complementary sheep and rat models in CIFASD

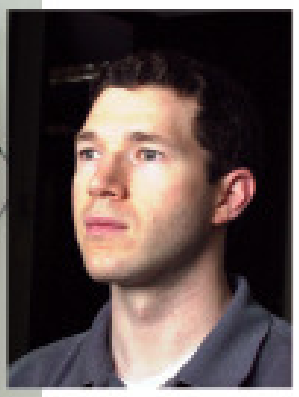
III. Earlier/Better Diagnosis

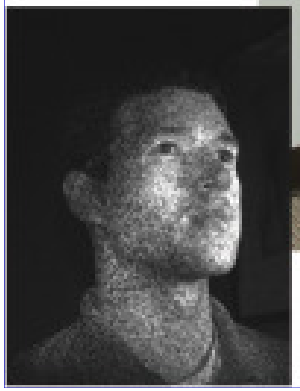
- To test training methods, imaging and earlier/more sensitive neurobehavioral testing measures to identify affected infants
  - Repeated physical examinations
  - Repeated prenatal ultrasound measures
  - 2-D and 3-D facial photographs
  - Repeated neurobehavioral testing

3D - facial imaging

Final 3D model constructed from the highest confidence data points.







1.5 Milliseconds

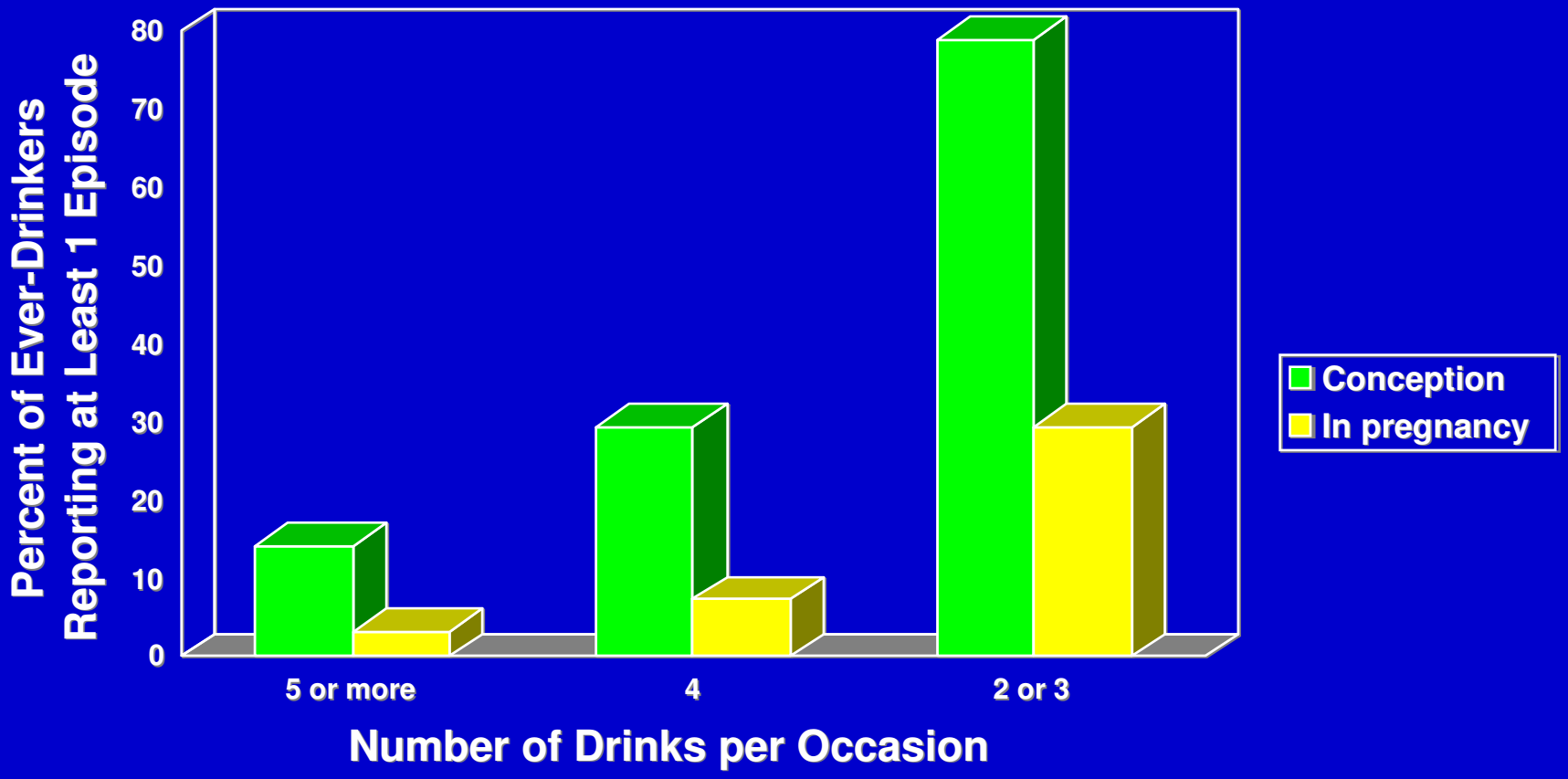
3-D facial imaging

Preliminary Findings

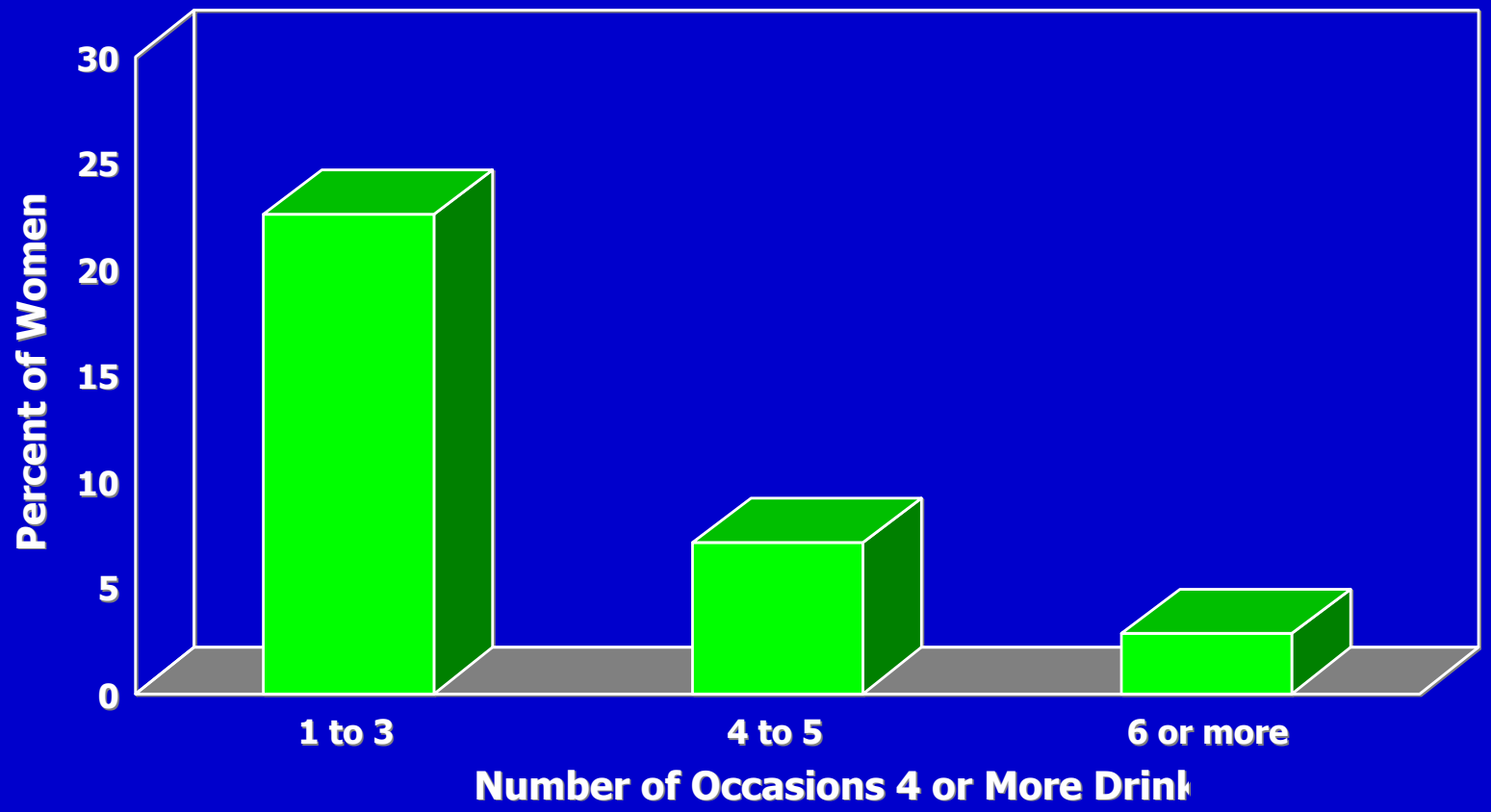
Maternal interviews - Russia

Characteristics N = 1164 Women Interviewed	Mean (SD) or proportion
Age (years)	25.2 (5.5)
Gestational age at enrollment (wks)	13.1 (6.9)
Current smokers	28.2%
Any alcohol month of conception	91.2%
Any alcohol most recent month	35.5%
Daily drinker month of conception	0.5%
Daily drinker most recent month	0.2%

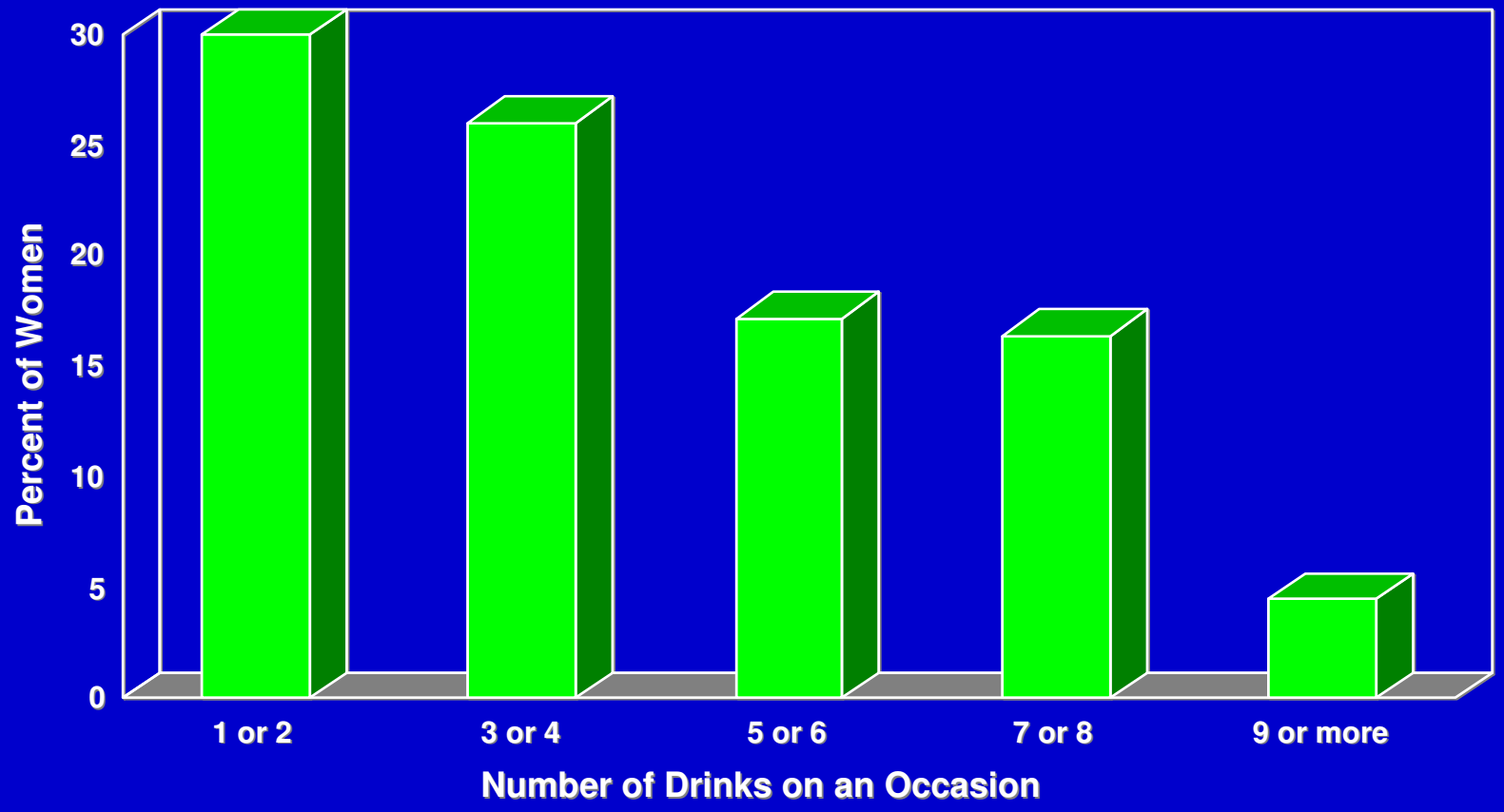
Any binge episodes - Russia



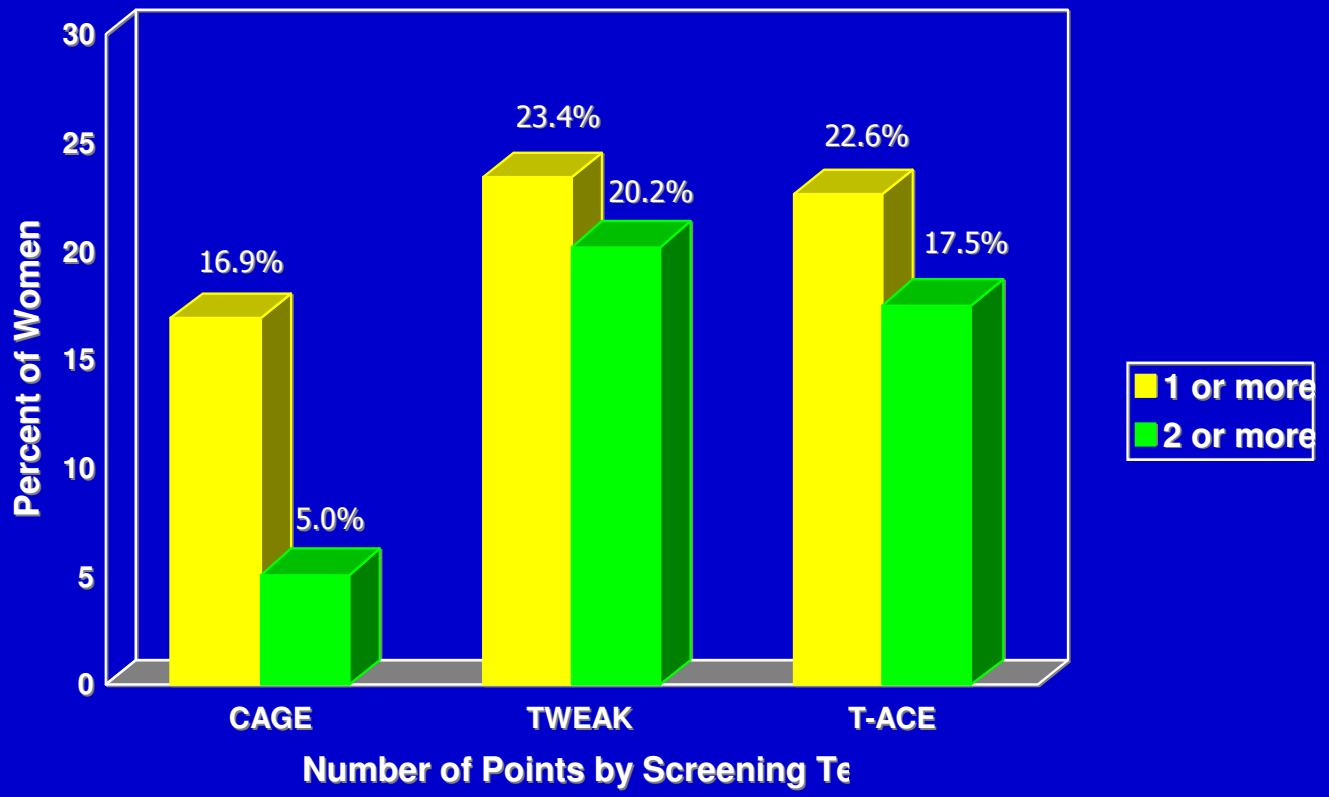
Number of binge episodes month around conception - Russia



Number of drinks can ‘hold’ - Russia



Signs of abuse in last year - Russia



Correspondence of signs of abuse for continued pregnancy drinking - Russia

Question	OR for continued drinking in pregnancy	95% CI	p-value
amnesia	16.98	4.00, 72.14	<0.001
annoy	3.94	0.76, 20.59	0.10
cut down	6.93	3.15, 15.25	<0.001
eye opener	1.63	0.19, 13.63	0.66
worry	4.21	1.45, 12.19	0.008
guilt	8.00	4.45, 14.38	<0.001

Correlation of maternal binge drinking with paternal drinking - Ukraine

Partner drinking	OR for mother's binge drinking (N = 166)	95% CI	p-value
Frequency			
<1 x week	1.0		<0.0001
1-2 x week	11.80	4.89, 28.44	
3-4 x week	32.44	8.88, 118.59	
Daily	12.17	1.79, 82.86	
Quantity			
1-2 drinks	1.0		<0.0001
3-4 drinks	8.57	3.55, 20.71	
≥5 drinks	39.00	12.20, 124.72	

Alcohol related physical features in newborns - Ukraine

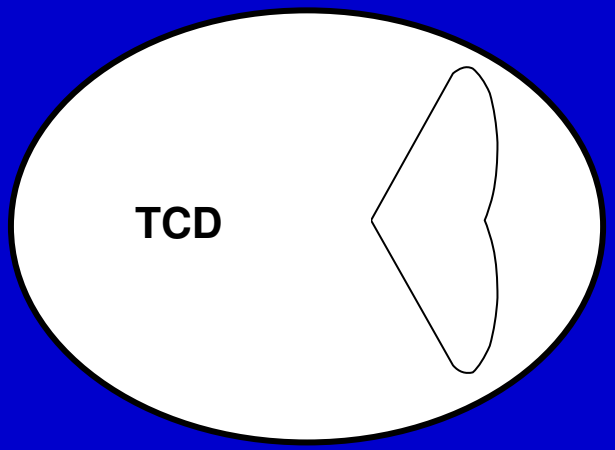
Feature - n (%)	Alcohol Exposed N = 67	No Alcohol N = 55	p-value
Palpebral fissures ≤10th centile	14 (21.2)	5 (9.1)	0.068
Smooth philtrum	10 (15.2)	2 (3.6)	0.035
Thin vermilion border	11 (16.7)	4 (7.3)	0.118
Hockey stick crease	4 (6.0)	0	0.126
Birth weight ≤10th centile	4 (6.0)	3 (5.5)	1.000
Birth length ≤10th centile	6 (9.0)	0	0.032
Birth head circumference ≤10th centile	4 (6.0)	0	0.126
FAS	3 (4.5)	0	
Some features of FAS	13 (19.4)	5 (9.1)	0.031

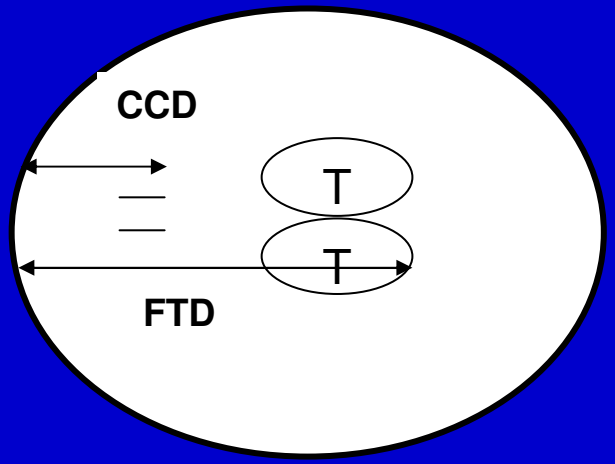
Minerals in Binge-Drinking Women vs. Unexposed - Russia

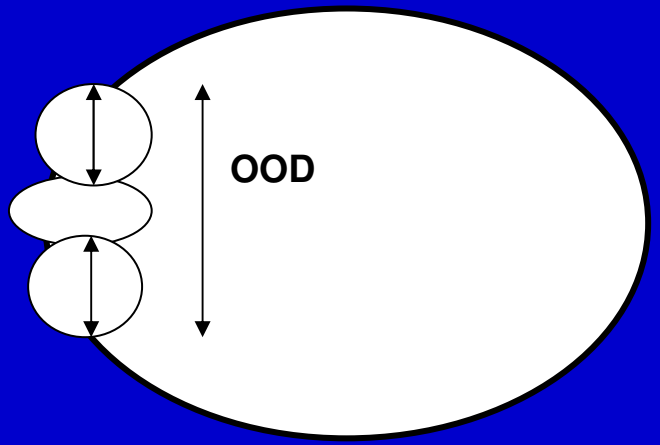
	1st/2nd trimester N = 20			3rd trimester N = 20		
Mineral	Alc+	Alc-	P-value	Alc+	Alc-	P-value
Ca	88.5	93.8	0.35	88.8	96.8	0.19
Cu	2.2	2.4	0.41	2.0	2.6	0.04
Fe	1.4	1.1	0.35	1.0	1.2	0.55
Mg	18.1	19.0	0.49	17.8	19.0	0.31
Se	0.11	0.13	0.17	0.11	0.14	0.15
Zn	0.59	0.73	0.08	0.62	0.78	0.01

Prenatal ultrasound brain measures - Ukraine

- Transverse Cerebellar Diameter
- Occipital Frontal Diameter
- Caval-Calvarial Distance
- Frontothalamic Distance
- Outer Orbital Distance
- Interorbital Distance
- Orbital Distance







Fetal growth measures (2nd trimester) FAS/some features vs. no FAS - Ukraine sample

Fetal Growth Measures*	FAS/D (n=21)	No FAS (n=121)	p-value
	Mean±sd	Mean±sd	
Estimated fetal wt percentile	27.6±4.2	35.0±1.8	0.105
Biparietal diameter percentile	47.0±7.1	56.1±2.9	0.236
Head circumference percentile	28.5±4.4	41.9±1.8	0.006
Abdominal circumference percentile	27.2±7.6	43.3±3.2	0.053
Femur length percentile	47.0±5.4	62.5±2.2	0.010

* All models adjusted for smoking

Fetal growth measures (3rd trimester) FAS/some features vs. no FAS - Ukraine sample

Fetal Growth Measures*	FAS/D (n=21)	No FAS (n=120)	p-value
	Mean±sd	Mean±sd	
Estimated fetal wt percentile	24.2±4.0	33.4±2.3	0.054
Biparietal diameter percentile	48.9±7.0	66.7±4.2	0.033
Head circumference percentile	33.9±5.6	53.8±3.3	0.003
Abdominal circumference percentile	47.3±6.3	54.2±3.5	0.350
Femur length percentile	30.9±6.3	51.9±3.6	0.005

* All models adjusted for smoking

Fetal brain measures (3rd trimester) FAS/some features vs. no FAS - Ukraine sample

Brain Measure	FAS/D (N=21)	No FAS (N=120)	p-value*
	Mean±s.e.	Mean±s.e.	
Transverse Cerebellar Diameter (mm)	40.8±0.4	41.9±0.5	0.178
Occipital Frontal Diameter (mm)	107.4±2.5	107.8±1.5	0.888
Caval-Calvarial Distance (mm)	41.6±1.0	43.3±0.6	0.127
Frontothalamic Distance (mm)	63.9±1.2	66.3±0.7	0.080
Outer Orbital Diameter (mm)	54.0±0.9	55.5±0.6	0.180
Interorbital Distance (mm)	14.9±0.6	15.6±0.3	0.301
Orbital Diameter (mm)	16.8±0.4	16.9±0.3	0.880

* Adjusted for gestational age & smoking in pregnancy

Conclusions

- Accurate diagnoses can be made in the newborn period offering opportunity for early intervention
- Nutritional factors may be important in FASD (and potentially modifiable)
- Prenatal ultrasound may have clinical relevance in identifying alcohol-affected fetuses in mid-gestation

Future plans

- Explore better maternal biomarkers
- Link early identification of high risk infants to initiation of early treatment