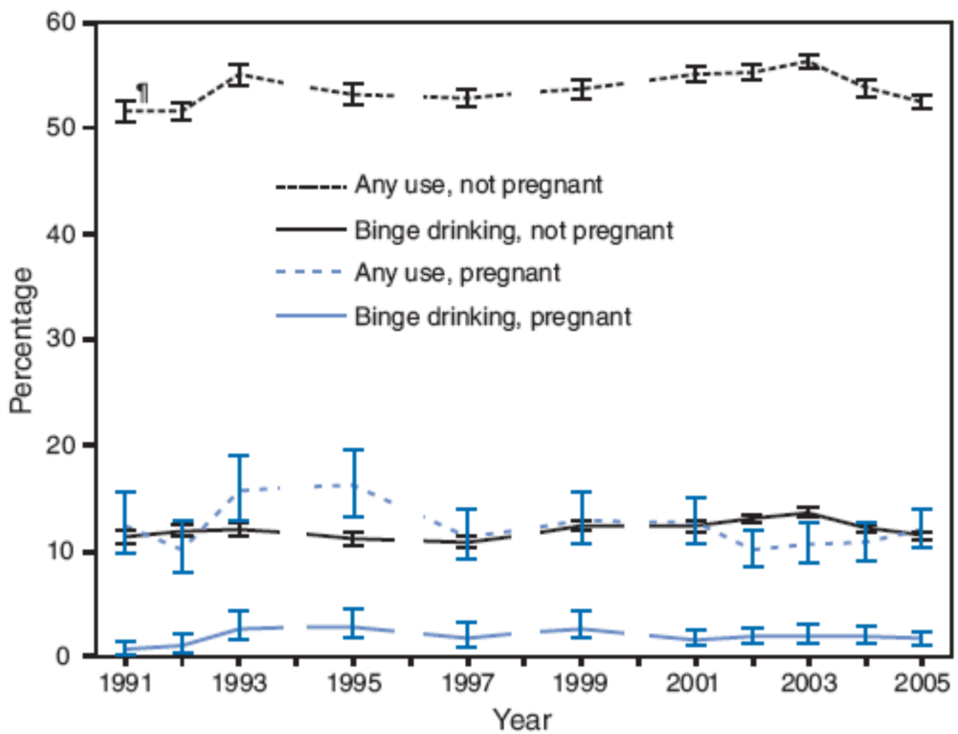
Preventing the Preventable: Where Do We Stand on Fetal Alcohol Spectrum Disorders in 2016?

Christina Chambers, PhD, MPH
University of California San Diego
Robert L. Brent Lecture
Teratogen Update

CENTER for BETTER BEGINNINGS

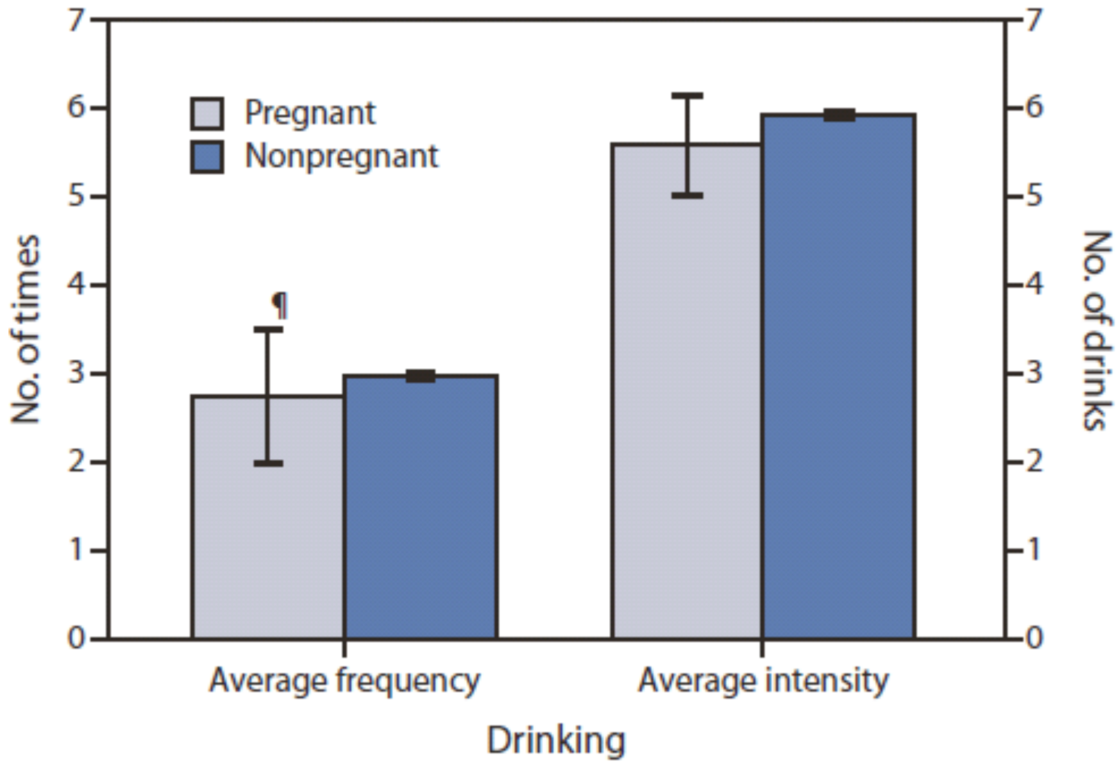
UC San Diego
SCHOOL OF MEDICINE

Prevalence of Alcohol Consumption



Last 30 days women 18-44; 1991-2005; *MMWR* 2009;58:529

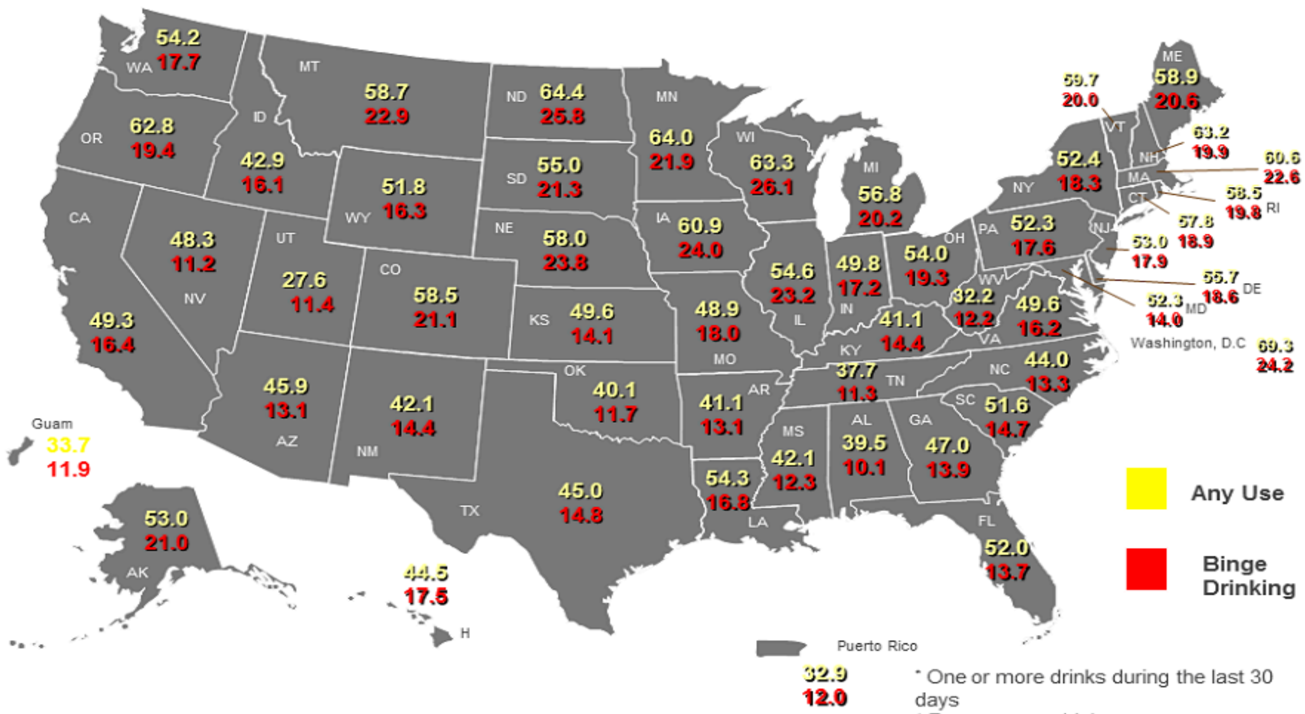
Binge Episodes ≥ 4 Drinks



Last 30 days women 18-44 who binged; 2006-2010; *MMWR* 2012;61:534

Fast Forward: 2013

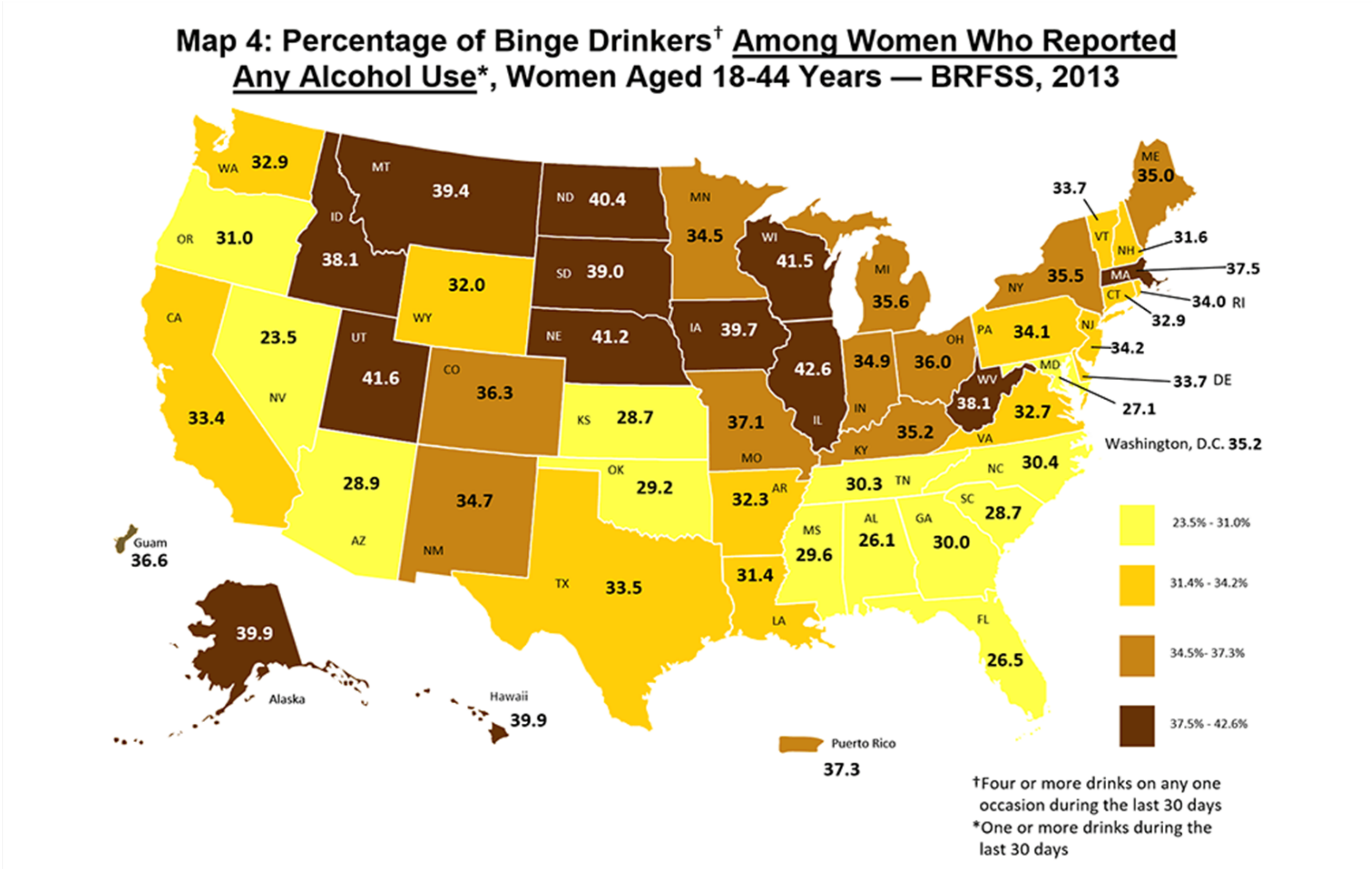
Map 1: State-Specific Weighted Prevalence Estimates of Alcohol Use (Percentage of Any Use* & Binge Drinking†) Among Women Aged 18 – 44 Years — BRFSS, 2013



* One or more drinks during the last 30 days

† Four or more drinks on any one occasion during the last 30 days

Fast Forward: 2013



Prevalence of Fetal Alcohol Spectrum Disorders

ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

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Critical Review

Worldwide Prevalence of Fetal Alcohol Spectrum Disorders: A Systematic Literature Review Including Meta-Analysis

Sylvia Roozen, Gjalt-Jorn Y. Peters, Gerjo Kok, David Townend, Jan Nijhuis, and Leopold Curfs

Background: Although fetal alcohol spectrum disorders (FASD) affect communities worldwide, little is known about its prevalence. The objective of this study was to provide an overview of the global FASD prevalence.

Methods: We performed a search in multiple electronic bibliographic databases up to August 2015, supplemented with the ascendancy and descendancy approach. Studies were considered when published in English, included human participants, and reported empirical data on prevalence or incidence estimates of FASD. Raw prevalence estimates were transformed using the Freeman–Tukey double arcsine transformation so that the data followed an approximately normal distribution. Once the pooled prevalence estimates, 95% confidence intervals and prediction intervals were calculated based on multiple meta-analyses with transformed proportions using random effects models, these estimates were transformed back to regular prevalence rates. Heterogeneity was tested using Cochran's Q and described using the I^2 statistic.

Results: Among studies that estimated prevalence in general population samples, considerable differences in prevalence rates between countries were found and therefore separate meta-analyses for country were conducted. Particularly high-prevalence rates were observed in South Africa for fetal alcohol syndrome (55.42 per 1,000), for alcohol-related neurodevelopmental disorder (20.25 per 1,000), and FASD (113.22 per 1,000), For partial fetal alcohol syndrome high rates were found in Croatia (43.01 per 1,000), Italy (36.89 per 1,000), and South Africa (28.29 per 1,000). In the case of alcohol-related birth defects, a prevalence of 10.82 per 1,000 was found in Australia. However, studies into FASD exhibited substantial heterogeneity, which could only partly be explained by moderators, most notably geography and descent, in meta-regressions. In addition, the moderators were confounded, making conclusions as to each moderator's relevance tentative at best.

& EXPERIMENTAL RESEARCH

U.S. Prevalence Estimates: NIH-NIAAA CoFASP Consortium 2011-2016

- Common ascertainment methods among population-based samples of first grade children in 4 U.S. communities
- Common tools/protocols for assessing
  - Alcohol consumption in pregnancy
  - Physical features
  - Neurobehavioral performance

- Common diagnostic classification criteria

Hoyme et al, *Pediatrics*, in press

ARTICLE

Prevalence and Characteristics of Fetal Alcohol Spectrum Disorders

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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

NIH

FAS + pFAS 1.1-2.5%; FASD 2.4-4.8%

Pediatrics, 2014;134:855

What Can Be Done?

Prevention & Intervention

- Screening, referral and brief intervention in primary care for women of reproductive age
- Better biomarkers of exposure in pregnancy
- Earlier and more accurate diagnosis of affected children
- Understanding of potential protective/susceptibility factors that can lead to treatments or interventions
- Engagement of the medical community to recognize that FASD is not a rare phenomenon

Prevention & Intervention

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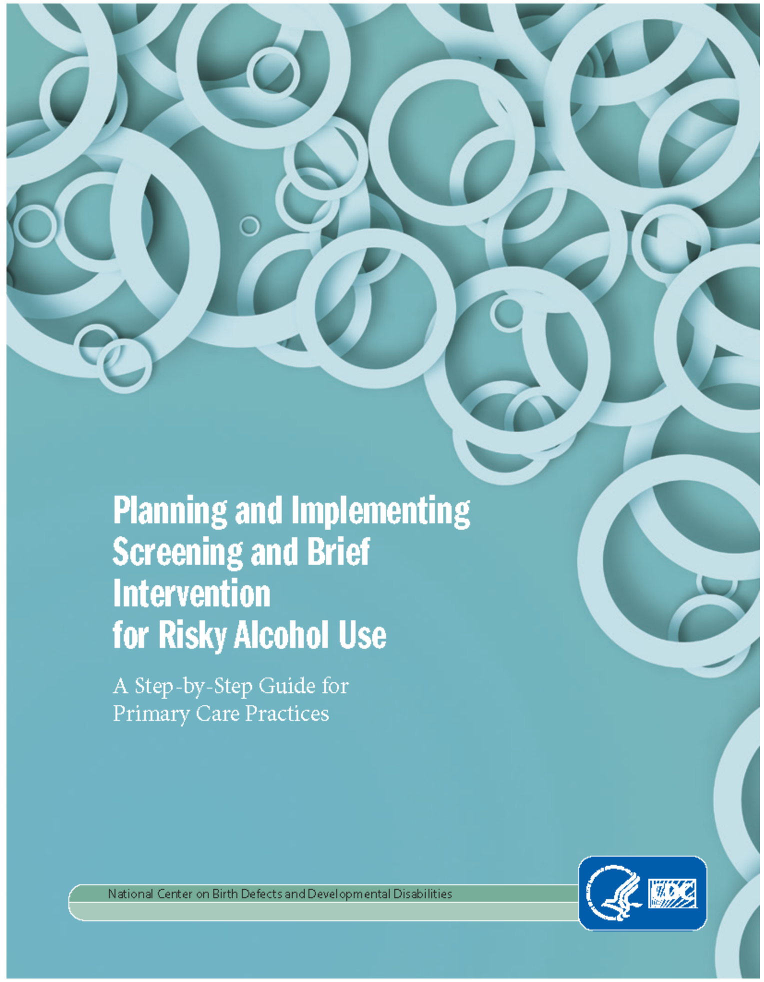

Planning and Implementing Screening and Brief Intervention for Risky Alcohol Use

A Step-by-Step Guide for Primary Care Practices

National Center on Birth Defects and Developmental Disabilities

CDC

Prevention & Intervention

- Screening, referral and brief intervention in primary care for women of reproductive age
- **Better biomarkers of exposure in pregnancy**
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CIFASD | Collaborative Initiative on Fetal Alcohol Spectrum Disorders

MISSION | RESEARCH | CENTER NEWS & EVENTS | PUBLICATIONS | CONTACT US | PRINCIPAL INVESTIGATORS | LINKS | CIFASD TRAINING

Latest News

- Imaging study sheds new light on alcohol-related birth defects
- Cognitive changes may be only sign of fetal alcohol exposure
- Functional neurologic abnormalities due to prenatal alcohol exposure are common

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

Ukraine Cohort Study

- Prospective pregnancy cohort, 2004-2017
- Collaboration with Omni-Net Centers in Ukraine
- Participants were recruited at Rivne Regional Medical Diagnostic Center and the Khmelnytsky Perinatal Center
- Moderate to heavily exposed women in early pregnancy and low/ unexposed women enrolled
- Blood samples collected 2^{nd} and 3^{rd} trimesters
- Physical evaluations for features of FASD and growth
- Neurobehavioral evaluations at 6 and 12 months and again at preschool age

Ukraine Cohort Study

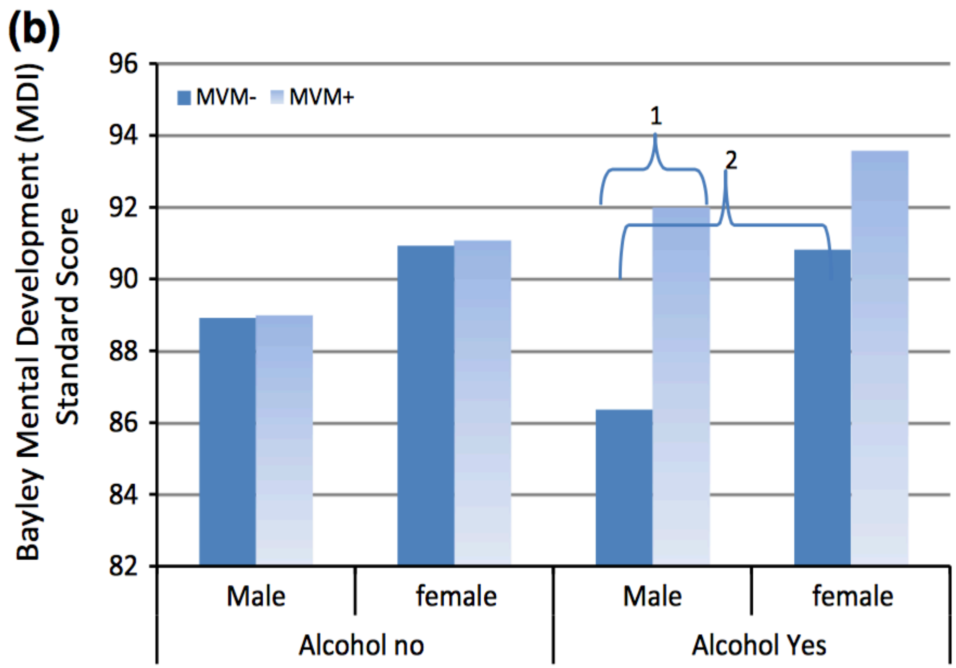
Ukraine Cohort Study

Ukraine Cohort Study – Protective Factors

Additional 750 mg choline supplement for 25%

Multivitamin/ mineral supplement provided for 50%

Bayley Scales of Infant Development MDI at 6 Months by Alcohol Group and by Micronutrient Supplement



[1]Mean difference: Supplement use= –5.64, df=1, p<.004, MMV+>MMV–

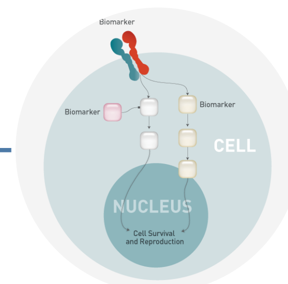
[2]Mean difference, Child Sex =–4.46, df=1, p<.024, girls> boys

Alcohol dose p <0.001

Coles et al, 2015 *Matern Child Health J*

Additional Questions

How do mothers who drink differ from mothers who do not?

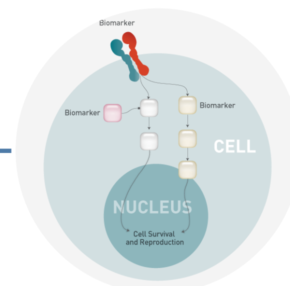


Biomarker of exposure

Could help with identifying who needs intervention

Additional Questions

How do mothers of FASD children differ from mothers who drink and have unaffected children?



Biomarker of effect

Could help with developing treatments

In What Ways Can We Address These Questions?

- Epigenetics: In mouse models of prenatal alcohol, evidence that epigenetic processes such as DNA methylation may underlie long-term changes in gene expression patterns
- MicroRNAs: In mouse models of prenatal alcohol, transcription may be further fine-tuned by altered microRNA expression

Kleiber Ml et al, *Frontiers in Genetics*, 2014

In What Ways Can We Address These Questions?

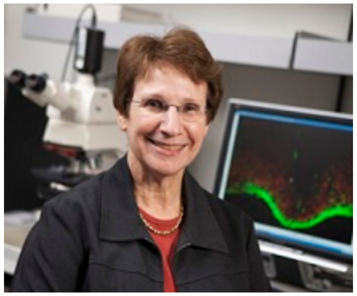
- MicroRNAs: One human study of 14 drinking mothers found specific serum microRNA expression significantly altered
- Inflammation: Inflammatory and stress markers are altered in mouse models of prenatal alcohol exposure

Gardiner AS et al, *Alcoholism Clin Exp Res*, 2016

Bodnar T et al, *Brain Beh and Immun,* 2016

Ukraine Cohort Study Design

- Nested case-control analysis
  - Group 1: HEa – Alcohol-Exposed with FASD affected child
  - Group 2: HEua – Alcohol-Exposed with unaffected child
  - Group 3: UE – Low or no alcohol exposure
- Three independent analyses of same datasets
  - Maternal methylation status (Kelly Frazer, UCSD) N’s = 19, 21, 55
  - Maternal miRNA status (Rajesh Miranda, Texas A&M) N’s = 22, 22, 23
  - Maternal inflammatory marker status (Joanne Weinberg, UBC) N’s = 35, 22, 95



Maternal Methylation Status
2nd and 3rd Trimester

Differential Methylation

- **Group 1 vs 2**
  - 9 significant CpGs
  - (padj < 0.05)
    - all Hypomethylated in Group 1
    - Genes: OR2A2, PCDHB17, LOC115110, TBC1D16, ITPK1
- **Group 1 vs 3**
  - 4 significant CpGs
  - (padj < 0.05)
    - Genes: ADARB2, PANX2

Differentially Methylated Genes – 1 vs 2

- OR2A1. PCDHB17, LOC115110, TBC1D16, ITPK1

Gene Identifiers Species: Hs

Symbol:	OR2A1
Description:	olfactory receptor, family 2, subfamily A, member 1
Accessions:	346528 (NCBI Gene) ENSG00000221970 (Ensembl) Q8NGT9 (UniProt) 110586 (HomoloGene)
Aliases:	
Genome Location:	chr7:144318125-144319057 (hg19)
Function:	Molecular Function G-protein coupled receptor activity (GO:0004930) olfactory receptor activity (GO:0004984) Biological Process G-protein coupled receptor signaling pathway (GO:0007186) detection of chemical stimulus involved in sensory perception of smell (GO:0050911) Cellular Component plasma membrane (GO:0005886) integral component of membrane (GO:0016021)
Interpro:	G protein-coupled receptor, rhodopsin-like (IPR000276) GPCR, rhodopsin-like, 7TM (IPR017452) Olfactory receptor (IPR000725)
Transcripts:	NM_001005287 XM_005249986 XM_005249987 ENST00000408951
Proteins:	NP_001005287 XP_005250043 XP_005250044 ENSP00000386175

OR2A1

From Wikipedia, the free encyclopedia

Olfactory receptor 2A1/2A42 is a protein that in humans is encoded by the *OR2A1* gene.[1]

Olfactory receptors interact with odorant molecules in the nose, to initiate a neuronal response that triggers the perception of a smell. The olfactory receptor proteins are members of a large family of G-protein-coupled receptors (GPCR) arising from single coding-exon genes. Olfactory receptors share a 7-transmembrane domain structure with many neurotransmitter and hormone receptors and are responsible for the recognition and G protein-mediated transduction of odorant signals. The olfactory receptor gene family is the largest in the genome. The nomenclature assigned to the olfactory receptor genes and proteins for this organism is independent of other organisms.[1]

Symbol:	PCDHB17
Description:	protocadherin beta 17 pseudogene
Accessions:	54661 (NCBI Gene) ENSG00000255622 (Ensembl)
Aliases:	ME4, PCDH-psi1
Genome Location:	chr5:141155996-141159061 (hg19)
Function:	
Interpro:	
Transcripts:	NR_001280 ENST00000539533 ENST00000623466
Proteins:	
Reporters:	GNF1H gnf1h01552_s_at HG-U133_Plus_2 216313_at 216355_at HG-U95Av2 1168_at

Symbol:	LOC115110
Description:	uncharacterized LOC115110
Accessions:	115110 (NCBI Gene) ENSG00000238164 (Ensembl)
Aliases:	
Genome Location:	chr1:2549920-2557031 (hg19)
Function:	
Interpro:	
Transcripts:	NR_026927 NR_037844 ENST00000416860 ENST00000432521 ENST00000443892 ENST00000448624 ENST00000449660 ENST00000452793
Proteins:	
Reporters:	HG-U133_Plus_2 232190_x_at 233960_s_at

Symbol:	TBC1D16
Description:	TBC1 domain family, member 16
Accessions:	125058 (NCBI Gene) ENSG00000167291 (Ensembl) Q8TBP0 (UniProt) 10380 (HomoloGene)
Aliases:	
Genome Location:	chr17:79932343-80035848 (hg19)
Function:	Molecular Function Rab GTPase activator activity (GO:0005097) protein binding (GO:0005515) Biological Process positive regulation of Rab GTPase activity (GO:0032851) regulation of cilium assembly (GO:1902017)
Interpro:	Rab-GTPase-TBC domain (IPR000195)
Transcripts:	NM_001271844 NM_001271845 NM_001271846 NM_019020 XM_005257049 XM_005257050 XM_005257052 XM_006721694 XM_006721695 ENST00000310924 ENST00000340848 ENST00000570373 ENST00000571872 ENST00000572862 ENST00000573782 ENST00000574241 ENST00000574427 ENST00000576768

Symbol:	ITPK1
Description:	inositol-tetrakisphosphate 1-kinase
Accessions:	3705 (NCBI Gene) ENSG00000100605 (Ensembl) ENSG00000274958 (Ensembl) Q13572 (UniProt) 601838 (OMIM) 8588 (HomoloGene)
Aliases:	ITRPK1
Genome Location:	chr14:92936914-93116320 (hg19) chrCHR_HSCHR14_7_CTG1:92936914-93115918 (hg19)
Function:	Molecular Function magnesium ion binding (GO:0000287) catalytic activity (GO:0003824) ATP binding (GO:0005524) isomerase activity (GO:0016853) inositol tetrakisphosphate 1-kinase activity (GO:0047325) inositol-1,3,4-trisphosphate 6-kinase activity (GO:0052725) inositol-1,3,4-trisphosphate 5-kinase activity (GO:0052726) inositol-1,3,4,5,6-pentakisphosphate 1-phosphatase activity (GO:0052825) inositol-1,3,4,6-tetrakisphosphate 6-phosphatase activity (GO:0052830) inositol-1,3,4,6-tetrakisphosphate 1-phosphatase activity (GO:0052831) inositol-3,4,6-trisphosphate 1-kinase activity (GO:0052835) Biological Process signal transduction (GO:0007165) blood coagulation (GO:0007596) phosphorylation (GO:0016310) dephosphorylation (GO:0016311) inositol trisphosphate metabolic process (GO:0032957) inositol phosphate metabolic process (GO:0043647) small molecule metabolic process (GO:0044281) Cellular Component cytosol (GO:0005829)
Interpro:	Inositol-tetrakisphosphate 1-kinase (IPR008656)
Transcripts:	NM_001142593 NM_001142594 NM_014216 ENST00000267615 ENST00000354313 ENST00000553452 ENST00000553655 ENST00000553695 ENST00000554999 ENST00000555495 ENST00000555553 ENST00000556185 ENST00000556603 ENST00000556954

ITPK1

From Wikipedia, the free encyclopedia

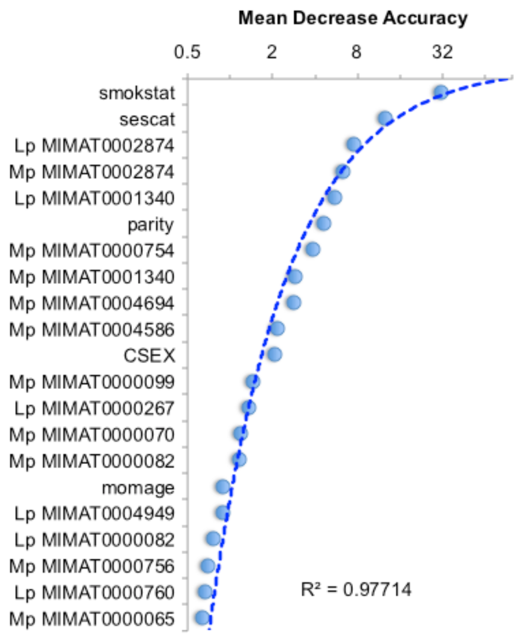
Inositol-tetrakisphosphate 1-kinase is an enzyme that in humans is encoded by the *ITPK1* gene.[1][2][3]

It is involved in inositol signalling pathways which regulate the conductance of calcium-activated chloride channels, and therefore could be relevant in the study of cystic fibrosis.[4][5]

Maternal miRNA Expression
2nd and 3rd Trimester

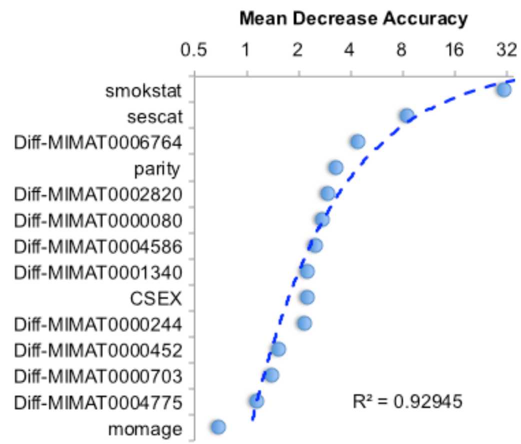
CENTER for BETTER BEGINNINGS

miRNA	MIMAT#	Exposure Group p<(BH)	UE		HEua		HEa	
			Mid Preg	Late Preg	Mid Preg	Late Preg	Mid Preg	Late Preg
hsa-miR-222-5p	MIMAT0004569	0.006						
hsa-miR-187-5p	MIMAT0004561	0.006						
hsa-miR-299-3p	MIMAT0000687	0.038						
hsa-miR-491-3p	MIMAT0004765	0.038						
hsa-miR-885-3p	MIMAT0004948	0.038						
hsa-miR-518f-3p	MIMAT0002842	0.038						
hsa-miR-760	MIMAT0004957	0.038						
hsa-miR-671-5p	MIMAT0003880	0.038						
hsa-miR-449a	MIMAT0001541	0.038						
hsa-miR-204-5p	MIMAT0000265	0.038						
hsa-miR-519a-3p	MIMAT0002869	0.038						
hsa-miR-363-3p	MIMAT0000707	0.065						
hsa-miR-378a-5p	MIMAT0000731	0.065						
hsa-miR-539-5p	MIMAT0003163	0.074						
hsa-miR-518b	MIMAT0002844	0.074						
hsa-miR-133b	MIMAT0000770	0.074						
hsa-miR-10b-5p	MIMAT0000254	0.074						
hsa-miR-517c-3p	MIMAT0002866	0.076						
hsa-miR-518e-5p	MIMAT0005450	0.076						
hsa-miR-524-3p	MIMAT0002850	0.088						
hsa-miR-147b	MIMAT0004928	0.097						



Top 5% high-variance miRNAs*,# Confusion Matrix for Group HEa *vs.* UE			
	Classified as HEa	Classified as UE	Classification error
True HEa	18	4	0.182
True UE	2	21	0.087

*With demographic and clinical variables. Overall mis-classification rate = 13.33
#Mid- and late-pregnancy miRNAs included in model as separate variables



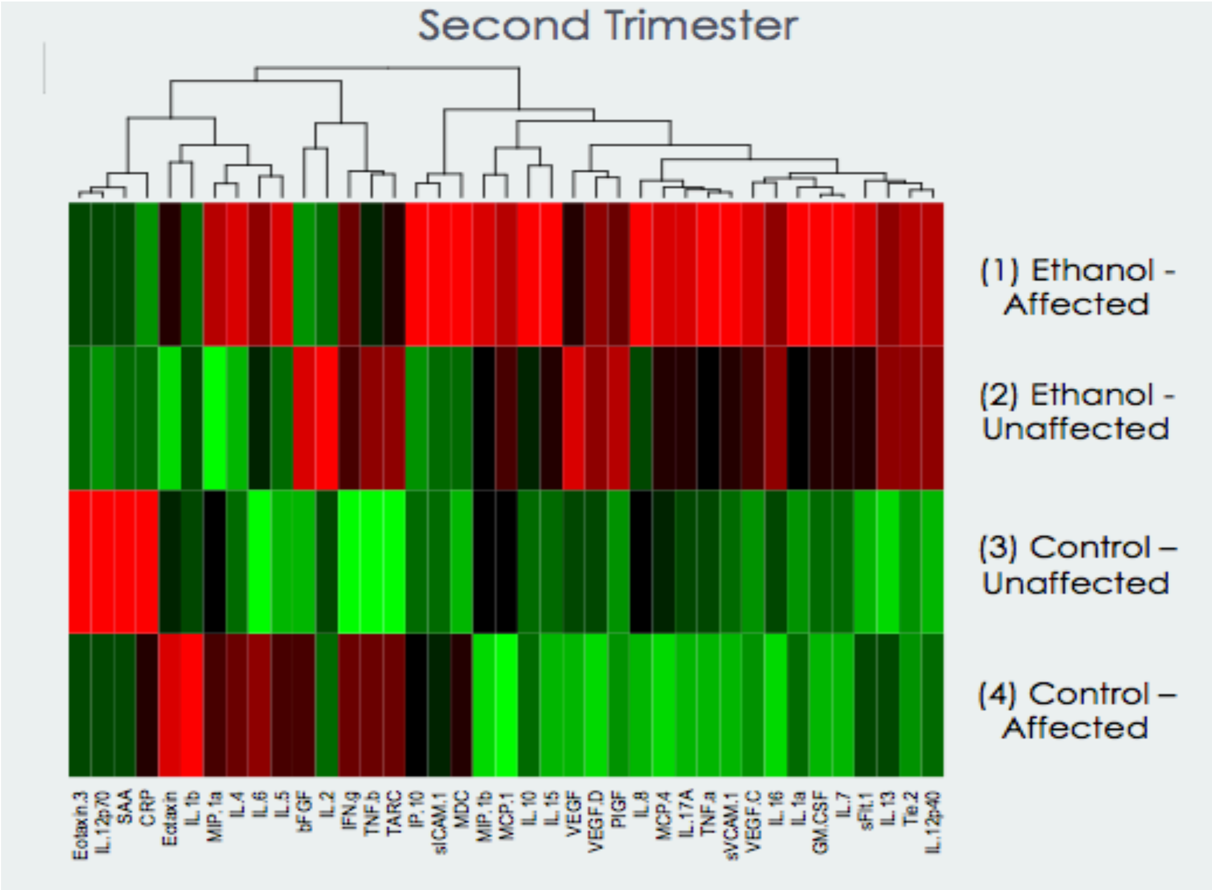
Top 5% high-variance miRNAs*,# Confusion Matrix for Group HEa *vs.* UE			
	Classified as HEa	Classified as UE	Classification error
True HEa	17	5	0.227
True UE	6	17	0.261

*With demographic and clinical variables. Overall mis-classification rate = 24.44
#Difference in expression between mid- and late-pregnancy miRNAs (ΔΔCT) included in model.

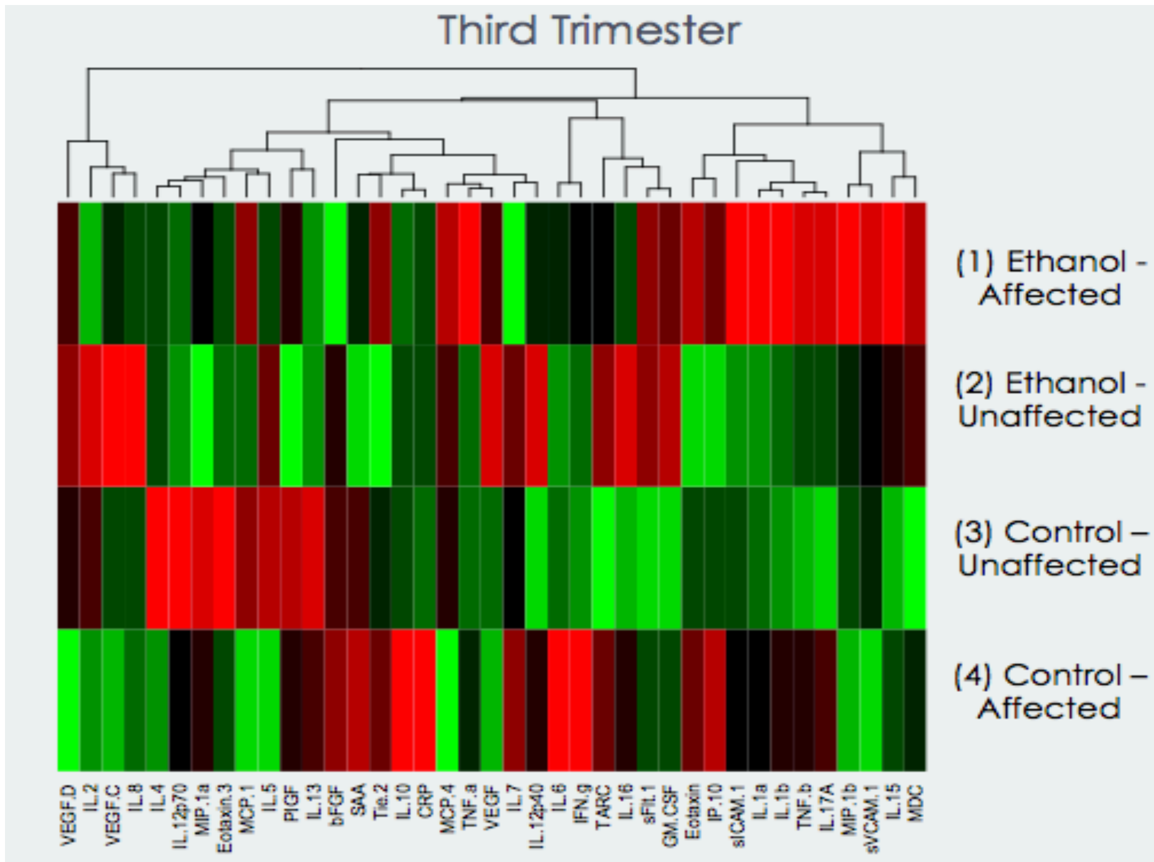
Maternal Markers of Inflammation 2nd and 3rd Trimester

Cytokines, Chemokines, Angiogenesis and Vascular Injury Markers

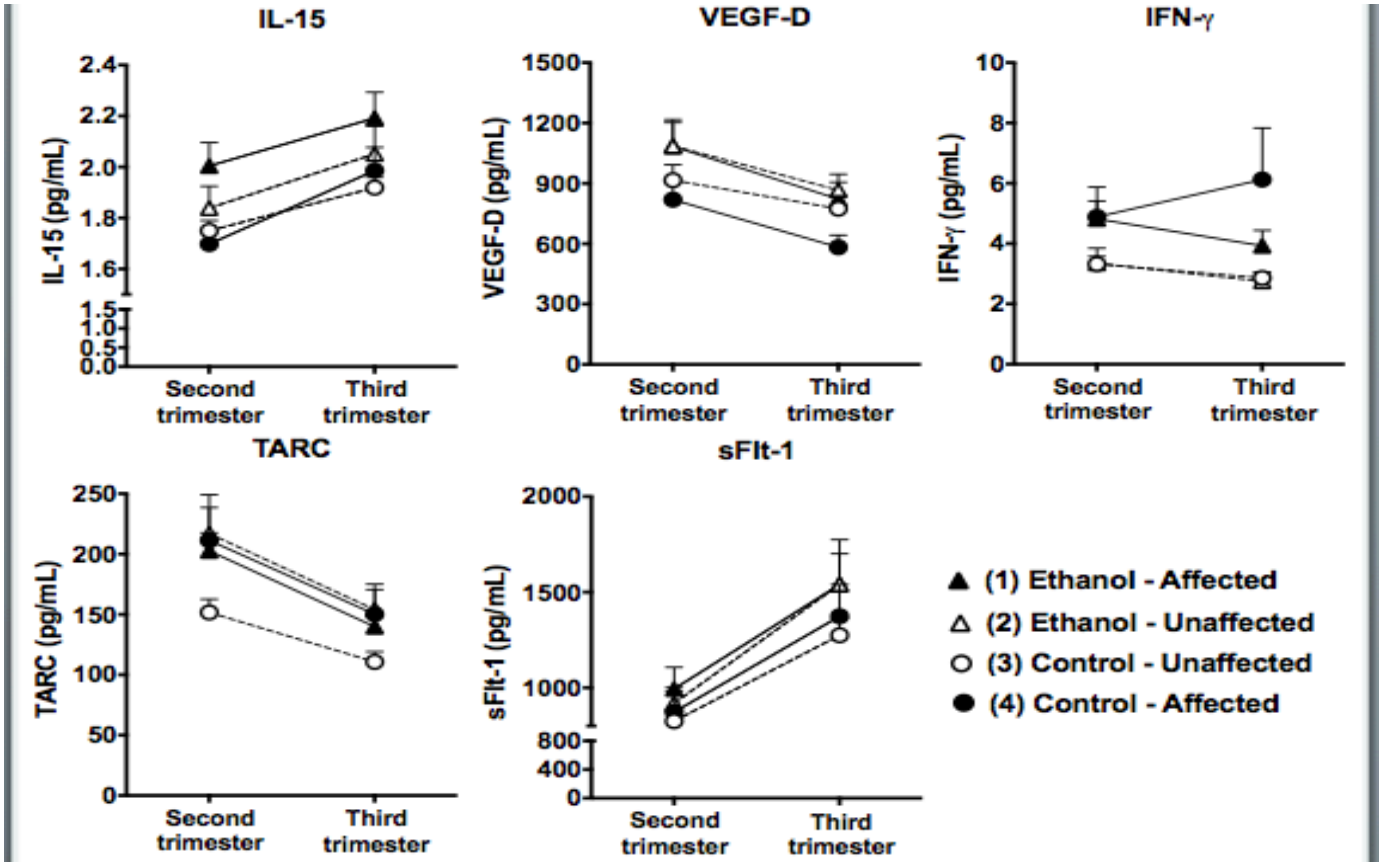
Heat Map 40 Analytes 2nd Trimester



Heat Map 40 Analytes 3rd Trimester



2nd to 3rd Trimester



Prevention & Intervention

- Screening, referral and brief intervention in primary care for women of reproductive age
- Better biomarkers of exposure in pregnancy
- Earlier and more accurate diagnosis of affected children
- Understanding of potential susceptibility factors that can lead to treatments/interventions
- **Engagement of the medical community to recognize that FASD is not a rare phenomenon**

CDC Practice and Implementation Centers (PIC)

- Regional initiative to increase awareness and skill level for various specialists
- In 2014, focus shifted from individual training for medical and allied health care professionals to impacting healthcare practice at the systems level and focusing on prevention opportunities
- National partnerships with AAP, ACOG, University of Pittsburgh School of Nursing, University of Texas Austin School of Social Work, and NOFAS

Our Challenge

Questions or Comments?