



FASD – a time for action!

Karen Moritz

Director, UQ Child Health Research Centre,
Centre for Children's Health Research



CARDD

Collaboration for Alcohol

Related Developmental Disorders

International FASD Awareness Day is observed every year on 9 September at 9:09am in recognition of the importance of being alcohol free for the nine months of pregnancy



The health of our children....

Australian children born today are less likely to be healthy adults and for the first time in history, have a shorter life expectancy than their parents.





Queensland Class of 2018

Pregnancy or
Birth complication

Allergy or asthma

Overweight/obese

Mental illness

Concussion

Fetal alcohol
spectrum disorder



Talks today



- Jan Hammill - The Year in review
- Natasha Reid – FASD: Clinical perspectives
- Lisa Akison – FASD: Animal research
- James Cuffe – Alcohol and nutrients during pregnancy
- Neroli Endacott – A caregivers perspective
- Wrap up, panel discussion, questions???



FASD Background

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FASD myths

- FASD is rare
- FASD is too hard or cannot be diagnosed
- They don't have 'the face', so they don't have FASD
- The damage is already done, so there is nothing we can do
- We don't need to worry about assessments, they will grow out of it

How common is FASD?

Recent U.S study

- Conservative prevalence estimate 1.13% to 5%
- Less conservative estimate 3.11% to 9.85%
- Only 2 of the 222 children identified had a previous FASD diagnosis!

W.A Lililwan study

- 19.4% of children diagnosed with FASD

To put these numbers into perspective

- Autism spectrum disorder 1.7%
- Cerebral palsy 0.15% to 0.4%

Rates are even higher in at-risk groups

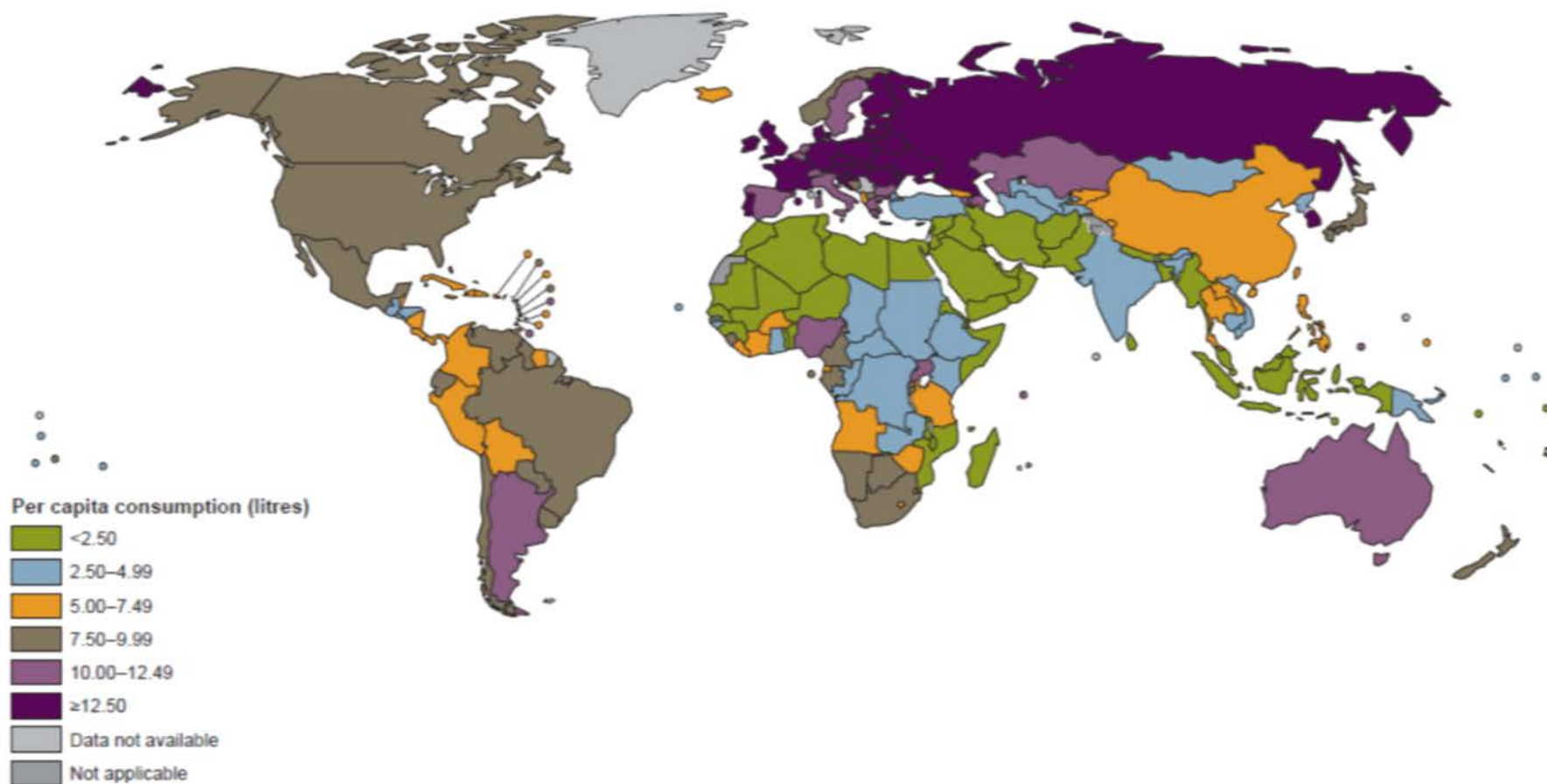
Prevalence among young people in WA detention

- 36% diagnosed with FASD
- 89% had at least one domain of severe impairment
- 74% of young people in detention were Indigenous

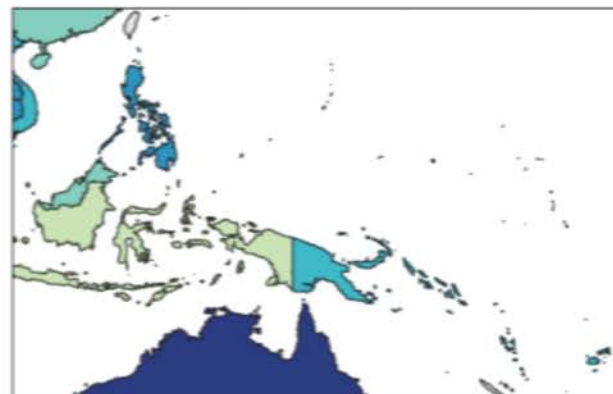
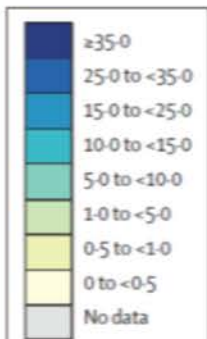
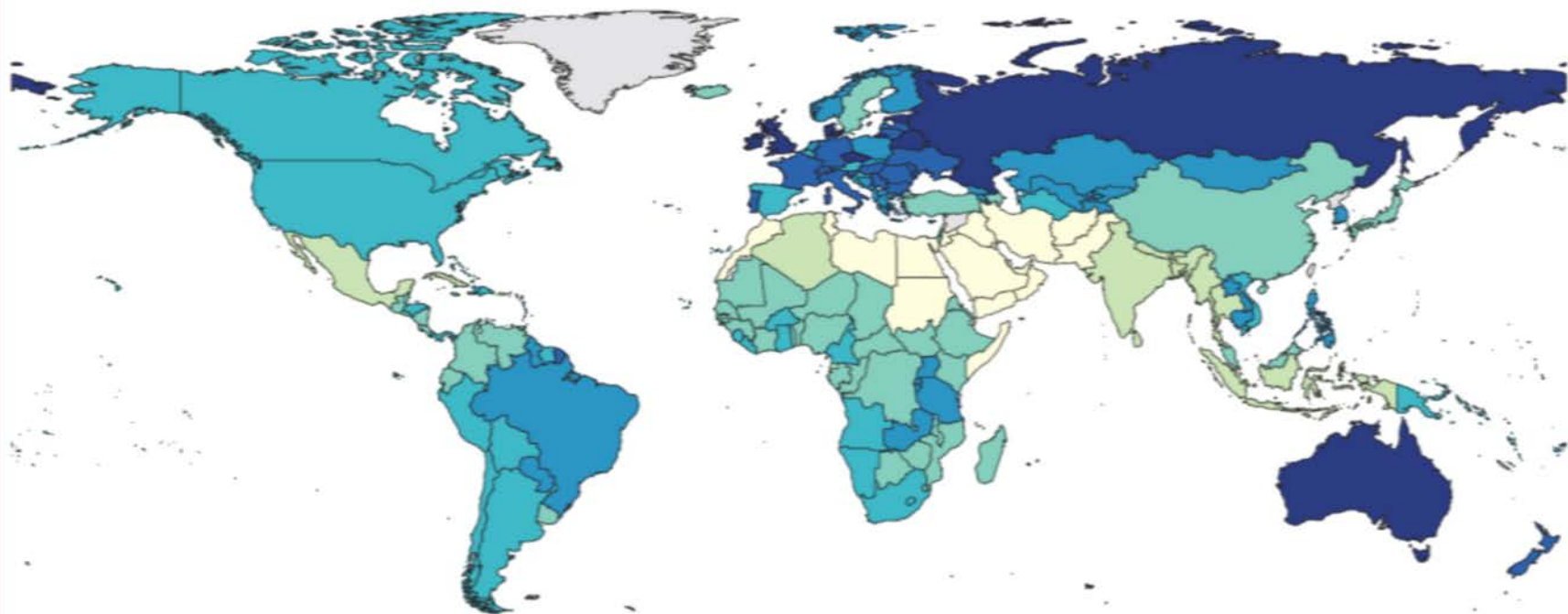
International prevalence of FASD in the out-of-home care system

- 16.9% of children and young people

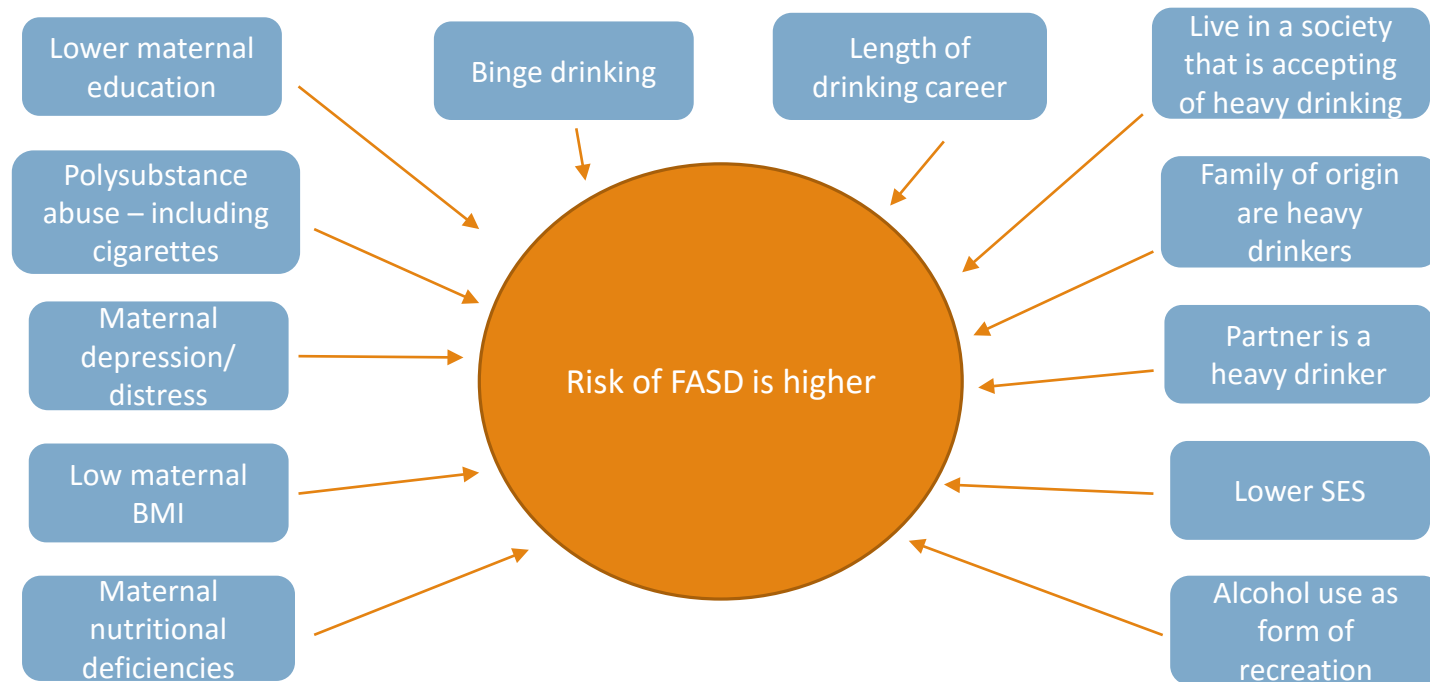
Figure 1. Total adult (15+) per capita consumption, in litres of pure alcohol, 2005^a



^a Best estimates of 2005 using average recorded alcohol consumption 2003–2005 (minus tourist consumption; see Appendix IV for details) and unrecorded alcohol consumption 2005.



FASD does not occur in isolation



Important that we remember to take a
no blame, no shame approach



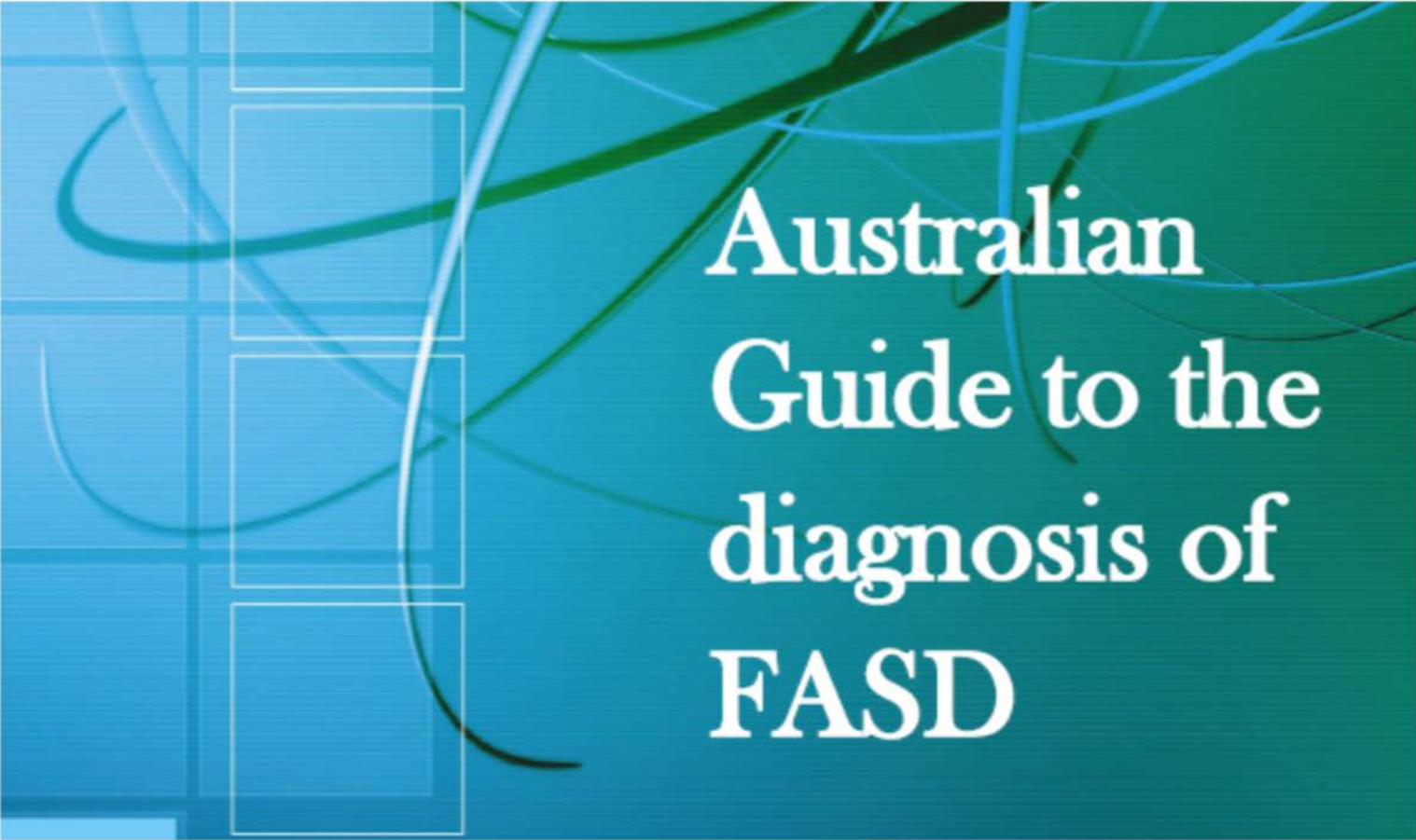
- Approximately 51% of Australian pregnancies are unplanned
- On average women find out they are pregnant at 6 weeks
- 80% of Australian women of reproductive age consume alcohol
- **60% reported consuming alcohol between conception and recognition**
- Approximately 1 in 4 women (25%) continue drinking after becoming aware of their pregnancy

The importance of FASD assessment and diagnosis

- Children are considered 'naughty' – without considering that they have an underlying brain injury
- The assessment helps us to properly understand how a child's brain is working and what supports they need to be successful
- Diagnosis creates understanding and compassion
- Every diagnosis raises awareness of FASD
- Potentially prevents future siblings experiencing prenatal alcohol exposure
- FASD is the number 1 cause of developmental disability in the world, but we can prevent this from happening

Quotes from caregivers

- “It shouldn’t take years to get a diagnosis when we could have been helping our kids and not wasting time. An early diagnosis can change things for us to start putting plans in place earlier”
- “A diagnosis means more than just another label”
- “ Just because the kids look fine, you can’t see inside their brain, this doesn’t mean they don’t have FASD”
- “Don’t give up on our kids putting them in the too hard basket”
- “You don’t have to be an alcoholic to have a child with FASD. I didn’t know I was pregnant till 6/9 weeks and didn’t touch alcohol at all after. My son was still born with FASD. It explains his whole childhood now I know”



Australian Guide to the diagnosis of FASD

Diagnostic criteria for FASD

	FASD with 3 sentinel facial features	FASD with < 3 sentinel facial features
Prenatal alcohol exposure	Confirmed or unknown	Confirmed
Neurodevelopmental domains	Severe impairment in at least 3 neurodevelopmental domains	Severe impairment in at least 3 neurodevelopmental domains
Sentinel facial features	Presence of 3 sentinel facial features	Presence of 0, 1 or 2 sentinel facial features

Prenatal alcohol exposure and health outcomes in offspring

Dr Lisa Akison

Developmental Programming Lab
School of Biomedical Sciences &
Child Health Research Centre



Defining DOHaD: Developmental Origins of Health and Disease

“Exposure of the fetus to a suboptimal environment causes adaptations that may help the fetus to survive in the short term, but leads to increased susceptibility of developing some diseases in adulthood.”



The DOHaD hypothesis

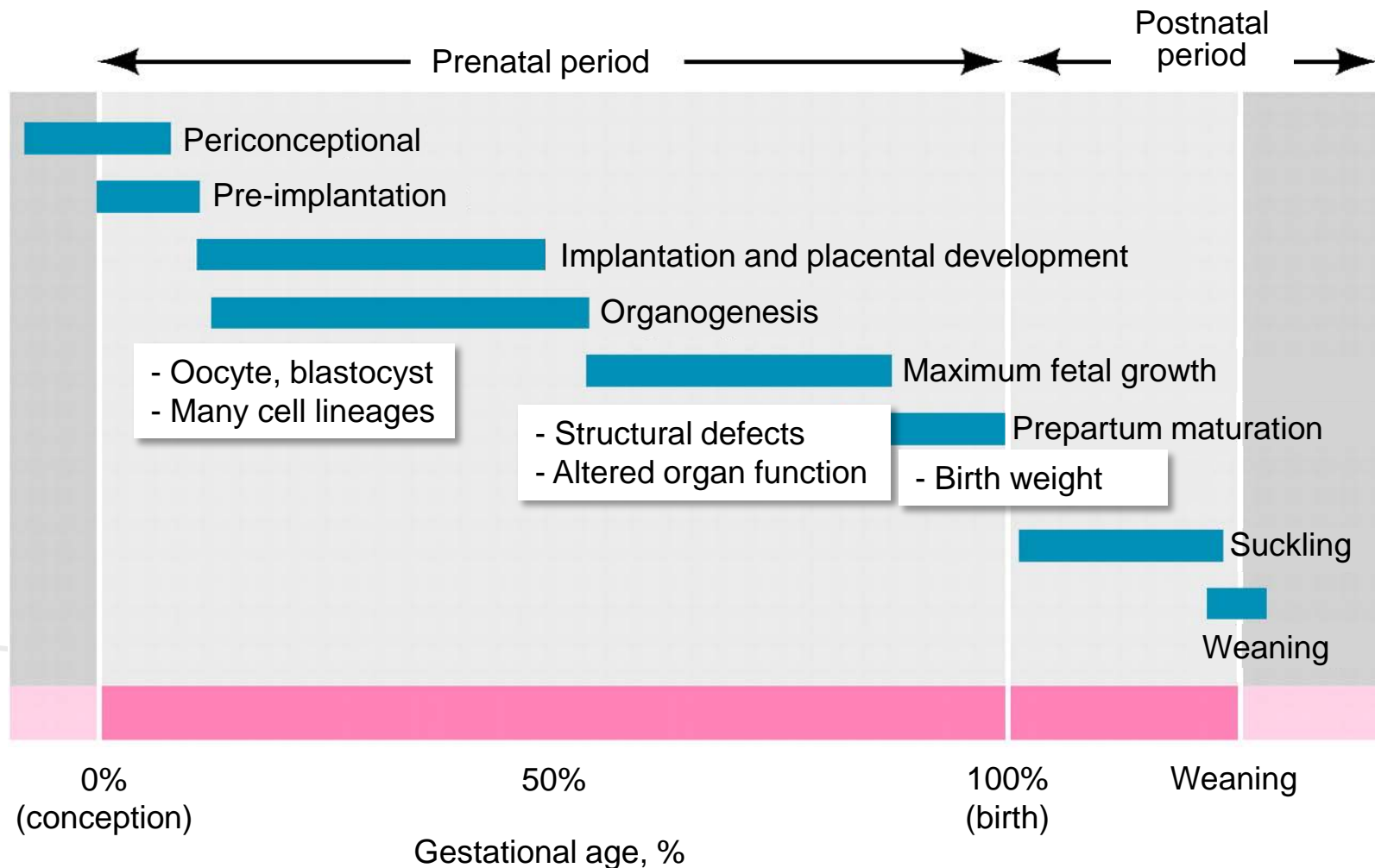
- **Suboptimal** intrauterine environment
- **Adaptation** to suboptimal conditions
- Physiological and morphological reprogramming
- Anticipation of limited resources
- **Mismatch** between the prenatal and post-natal environments
Growing up in the world of plenty!
- **Compensatory** growth
- **Cost:** chronic disease in later life



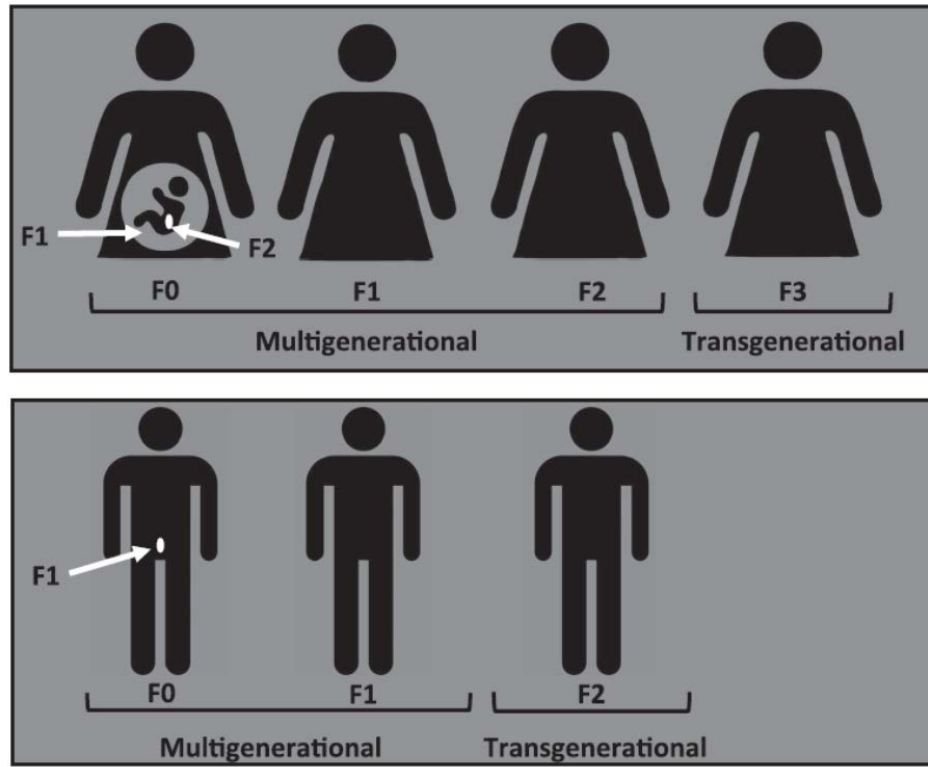
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DOHaD critical windows



Effects across generations



F0 F1 F2 F3

Need to consider maternal and paternal lines
Rodent is model of choice

Choice of species: Rat/mouse

Advantages:

- Easy to keep
- Short life span – great for multi-generational studies
- Placenta quite human-like
- Can do most physiology
- Molecular research tools
- Large litters so different outcomes can be measured
- Both males and females in each litter



Testing potential interventions/treatments



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Modelling human alcohol consumption – clinically relevant scenarios

Acute, high dose

- 2 days – weekend ‘binge’
- Pregnancy established but may not know...
- BAC - $\sim 0.12\%$



Chronic, low daily consumption

- Throughout entire pregnancy
- BAC- $\sim 0.03\text{-}0.04\%$

High dose, around conception **Very relevant model!**

- 4 days either side of conception
- BAC- $\sim 0.1\%$ (peak) then drops to $\sim 0.05\%$



Fetal and offspring growth

- Low birth weight (IUGR)
- Slowed growth or 'catch-up' growth during lactation
- Both males and females can be affected



Neurological effects

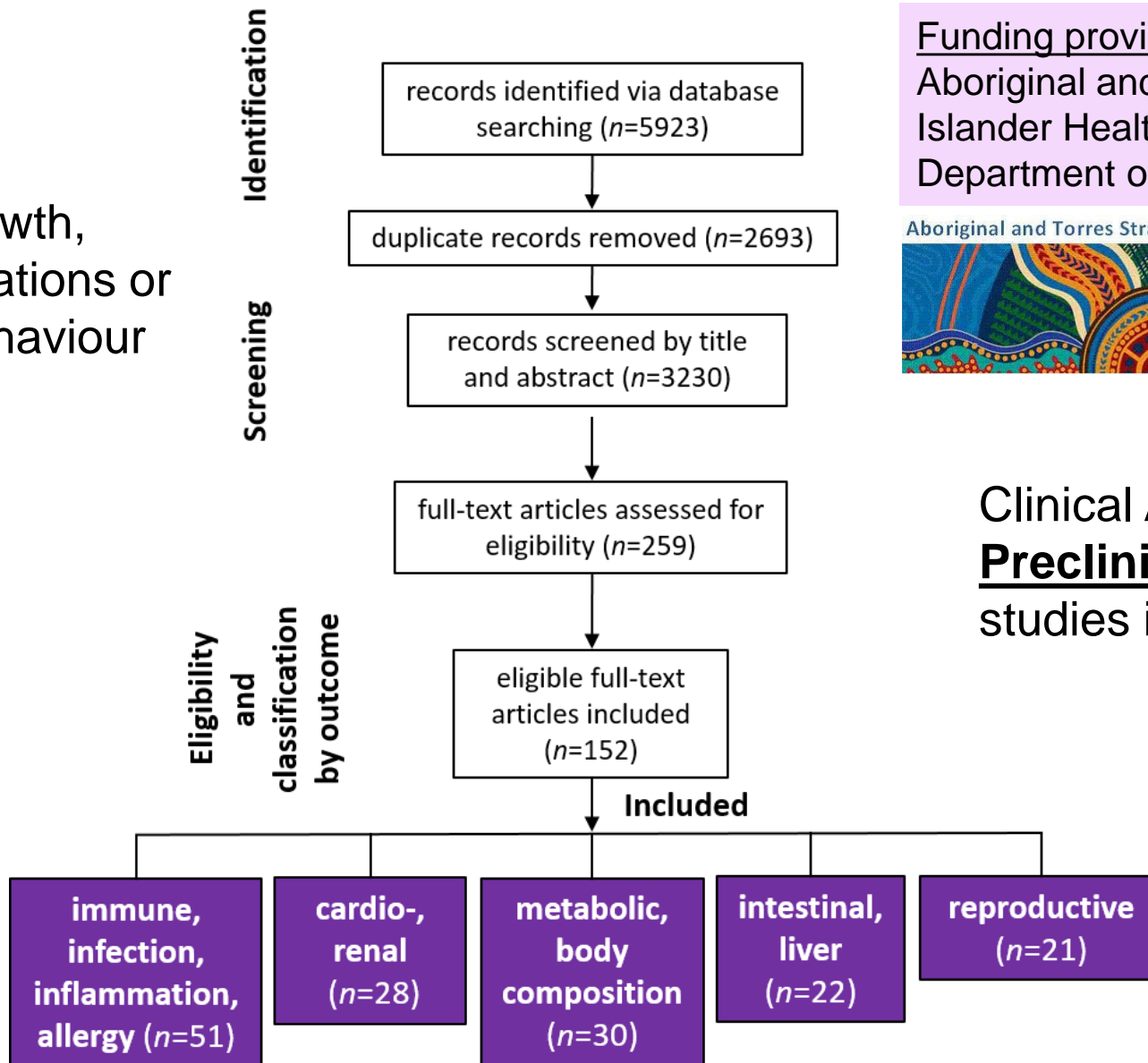
- Effects on brain and behaviour well known
- FAS, FASD, pFAS etc
- Learning and behavioural difficulties

**What diseases/health outcomes
can be programmed by prenatal
alcohol exposure?**



Systematic review of health outcomes following prenatal alcohol exposure

NOT growth, malformations or brain/behaviour



Funding provided by:
Aboriginal and Torres Strait
Islander Health Branch,
Department of Health, QLD

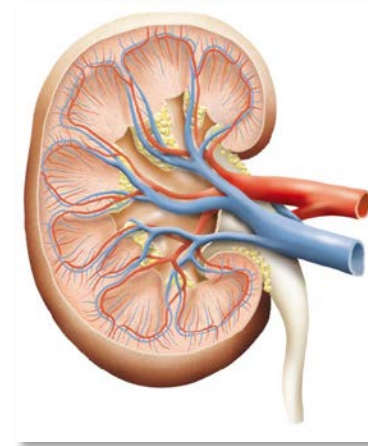
Aboriginal and Torres Strait Islander Health Unit



Clinical AND
Preclinical
studies included

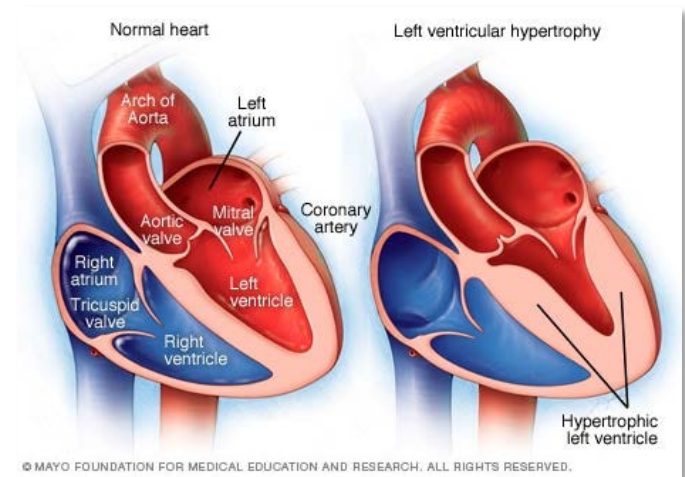
Renal function

- ↓ **nephron number**
= functional unit of the kidney
- Altered **filtering ability** of the kidney
- **Proteinuria** (sign of kidney damage) in males
- Effects worsened with age



Cardiovascular outcomes

- ***Hypertension*** – elevated blood pressure
- Enlargement of the wall of the left ventricle of the heart
- Reduced cardiac output



Metabolism & obesity

- Impaired ***glucose tolerance***
- ***Insulin resistance***
= Diabetic-like phenotype
- ↑ fasting glucose and insulin, particularly in males
- Worsened by:
 - Age
 - Postnatal high fat diet



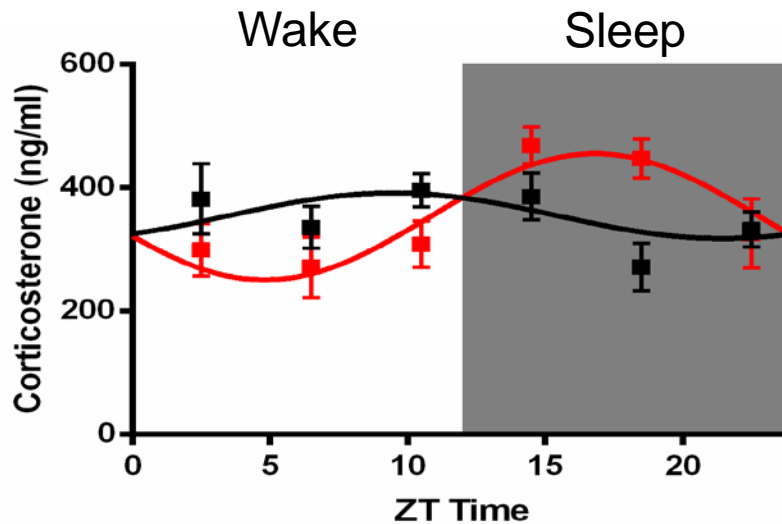
Metabolism & obesity

- ↑ **fat** in males (develop obesity)
- Altered hormones that regulate appetite (e.g. **leptin**)
- Dyslipidemia
- ↑ preference for a **high fat diet** in males

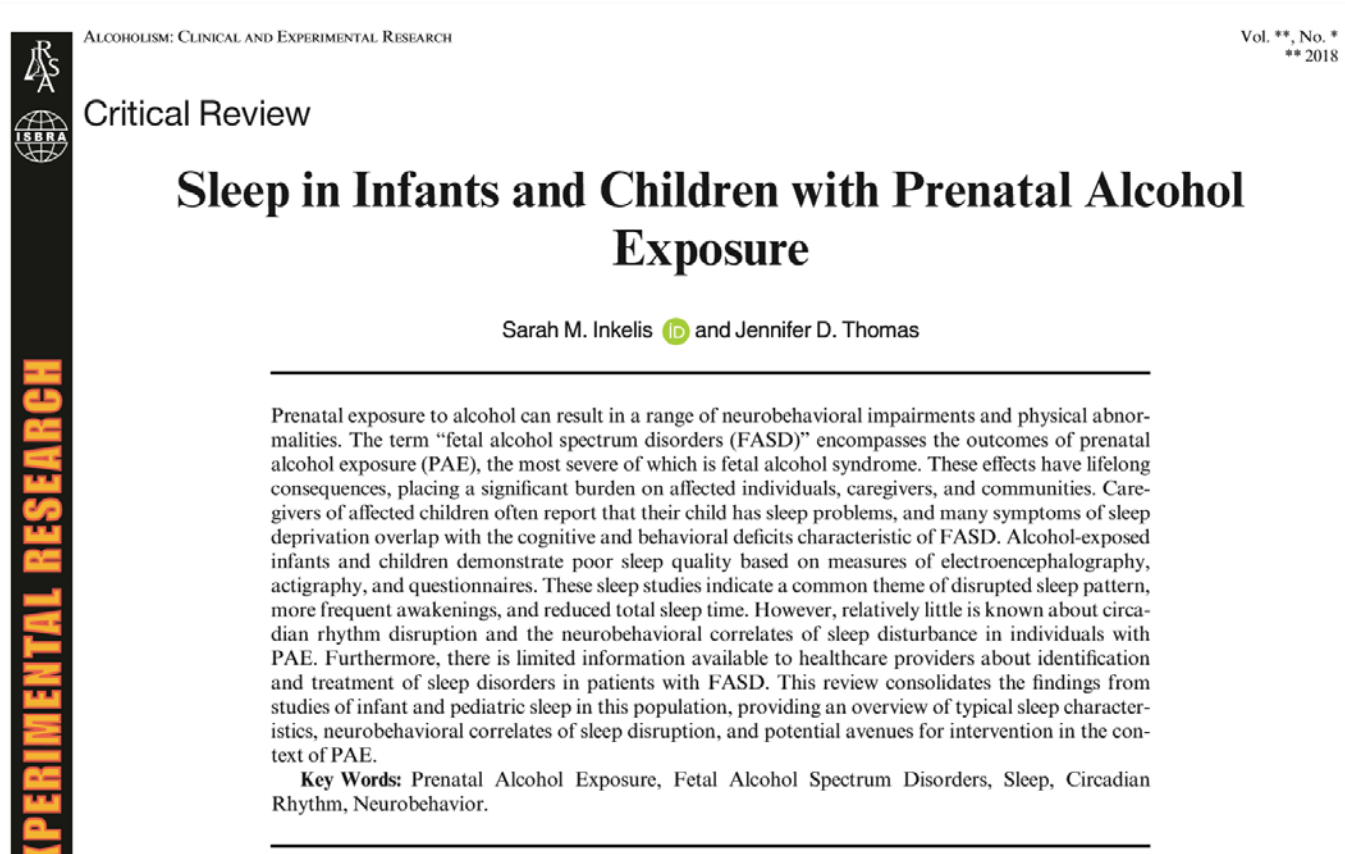


Circadian rhythms – altered sleep patterns?

- Alters stress hormone levels over 24h cycle, particularly in females
- Altered blood glucose levels in females

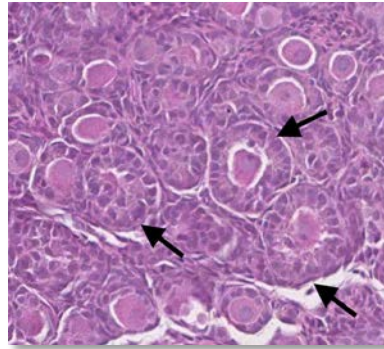


Recent review on PAE and sleep

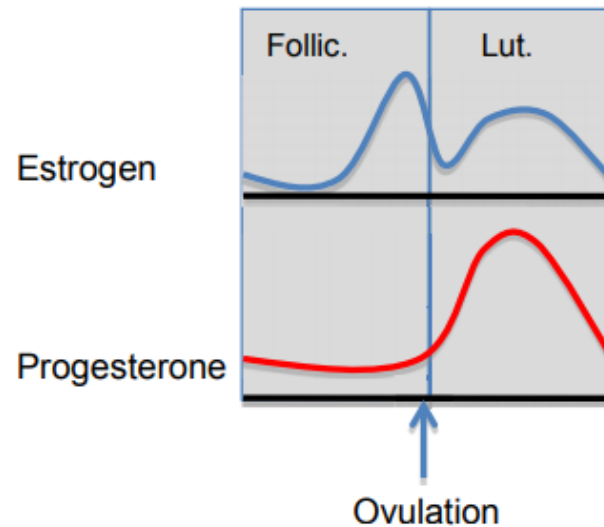


Male and female fertility

- Ovarian reserve
- Sperm counts
- Age at puberty
- Age at menopause
- Estrous cycles
- Hormone levels
- Breeding performance



Human menstrual cycle



Summary

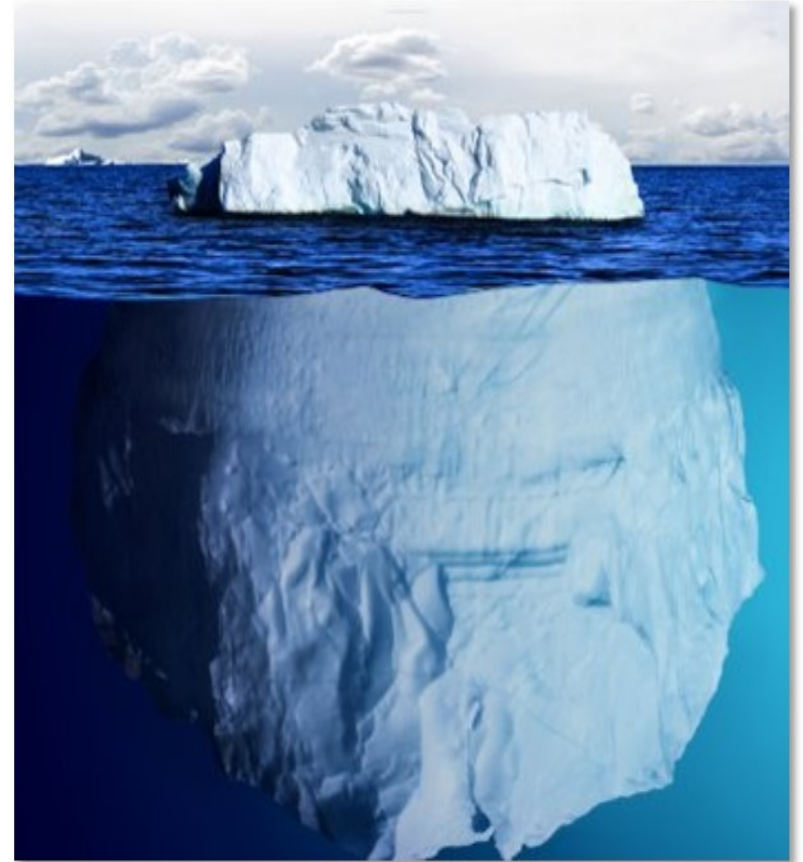
- Prenatal alcohol exposure can affect a variety of health outcomes in offspring
- Effects depend on:
 - Timing and severity of alcohol exposure
 - Sex of the baby/fetus
 - '2nd Hit' – e.g. aging or high fat diet



<http://www.marybacon.com/smoking-and-drinking-disasters-during-pregnancy/>

Brain outcomes...just the tip of the iceberg!

We need to be asking women about alcohol consumption during pregnancy and assessing all aspects of health in young people living with FASD



The role of micro nutrition in pregnancy outcomes: Impact of alcohol intake around pregnancy

Dr James Cuffe



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Why is nutrition relevant to FASD

Sociological / epidemiological

1. Many individuals are micronutrient deficient prior to pregnancy

2. Alcohol intake associated with dietary behaviours

Biological

3. Alcohol intake impairs intestinal absorption of micronutrients

4. Alcohol metabolism competitively utilises micronutrients



5. The effect of alcohol on development may be exacerbated by micronutrient deficiencies



The Australian Longitudinal Study on Women's Health

	All women *		Preconception characteristics of women who gave birth during the study †				p value‡
	Survey 1 (age 18–23 years [n=7047])	Survey 7 (age 37–42 years [n=6981])	Age at first birth				
			Age 18–25 years (n=544, 17.4%)	Age 26–30 years (n=1293, 41.5%)	Age 31–35 years (n=1024, 32.8%)	Age 36–42 years (n=257, 8.2%)	
Mean BMI (SD)	22.8 (4.2)	26.8 (6.4)	23.4 (4.8)	23.9 (4.4)	24.3 (4.5)	25.2 (5.6)	<0.0001
Overweight or obese	1340 (21.0%)	3223 (52.1%)	100 (27.2%)	342 (30.6%)	318 (34.0%)	94 (39.7%)	0.005
Deficient in Fruit and vegetable (<5 serves per day)	5861 (91.9%)	5659 (91.0%)	..	806 (91.9%)	533 (92.5%)	115 (86.5%)	0.13
Physical activity (<30 min/day)	1908 (37.7%)	2217 (43.3%)	249 (52.1%)	451 (38.8%)	318 (34.4%)	95 (41.1%)	<0.0001
Current smoker	1830 (27.9%)	685 (10.5%)	147 (28.0%)	227 (18.6%)	131 (13.4%)	35 (14.3%)	<0.0001
High risk alcohol intake §	348 (5.1%)	459 (6.9%)	17 (3.2%)	45 (3.6%)	49 (4.9%)	18 (7.1%)	0.008

§ Three or more standard drinks (10 g alcohol) on 5 or more days per week. Stephenson et al, Lancet, 2018



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As we obtain many of our micronutrients from fruit and vegetables, Many women likely to be deficient in key micronutrients

* Three or more standard drinks (10 g alcohol) on 5 or more days per week. † Stephenson et al., Lancet, 2016



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What are essential micronutrients and why are they important for our health?

- Micronutrients are nutrients obtained by food in very small quantities
- They are required for a large range of biological processes
- Overt deficiencies can lead to disease
- Subclinical deficiencies can impair normal physiology



Periconceptional Micronutrient intake

	Non-pregnant women of reproductive age (by age at survey)						
Lower reference nutrient intake		Total (N=509)	Age 18–25 years (n=156, 32%)	Age 26–30 years (n=79, 19%)	Age 31–35 years (n=102, 18%)	Age 36–42 years (n=172, 31%)	P value
Percentage with diet-only intakes below LRNI							
Vitamins							
Vitamin A	250 µg/day	7% (5–9)	12% (8–19)	5% (5–14)	2% (1–4)	5% (3–10)	0.002
Vitamin B12	1.0 µg/day	2% (1–3)	4% (2–8)	0	1% (0–3)	1% (0–6)	0.1
Folate	100 µg/day	4% (3–7)	8% (4–13)	1% (0–6)	0% (0–2)	5% (2–9)	0.003
Riboflavin	0.8 mg/day	14% (11–18)	22% (15–32)	11% (6–20)	9% (5–15)	11% (7–17)	0.03
Minerals							
Calcium	400 mg/day §	9% (7–12)	13% (9–20)	6% (3–14)	6% (3–12)	9% (5–14)	0.2
Iodine	70 µg/day	15% (11–19)	22% (15–31)	13% (7–23)	7% (4–14)	11% (7–18)	0.02
Iron	8.0 mg/day	30% (25–34)	38% (29–47)	26% (17–37)	23% (16–32)	27% (21–35)	0.09
Potassium	2000 mg/day	20% (25–34)	41% (32–51)	26% (17–38)	10% (12–28)	25% (19–33)	0.003
Selenium	40 µg/day	51% (47–56)	57% (47–66)	37% (26–49)	52% (42–62)	54% (46–61)	0.08
Zinc	4 mg/day	4% (3–7)	6% (3–11)	3% (1–9)	4% (2–9)	4% (2–9)	0.7

However, each of the other micronutrients have been shown to deficient around pregnancy in specific populations



While alcohol is the sole cause of FASD, what role may micronutrients play in exacerbating outcomes?

Is one of the reasons that some women exposed to alcohol have children with adverse outcomes while others do not, related to specific micronutrients ?



Behaviors linking Alcohol consumption and food quality

- There is a clear role of socioeconomic status that relates to severity of FASD outcomes- Could this be related to food quality or micronutrient intake?

	Children with FASD(n = 57)		Exposed controls(n = 42)		Unexposed controls(n = 106)		p-value
Demographic and socioeconomic variables							
Age on day of interview (yrs)—mean (SD)	36.1	(7.1)	33.1	(5.8)	34.2	(5.9)	.054
Height (cm)—mean (SD)	154.8	(5.9)	155.4	(10.6)	157.6	(6.0)	.037 ^b
Weight (kg)—mean (SD)	54.5	(14.7)	61.9	(13.1)	68.8	(18.8)	<.001 ^{a,b,c}
Head circumference (cm)—mean (SD)	54.8	(1.9)	54.9	(2.0)	54.8	(1.7)	.986
Body mass index (BMI)—mean (SD)	22.7	(5.6)	25.2	(5.2)	27.7	(7.5)	<.001 ^b
Residence during index pregnancy (%)							
Rural	71.4		50.0		25.5		<.001
Urban	28.6		50.0		74.5		
Educational attainment at interview (yrs)—mean (SD)	5.0	(2.8)	6.9	(3.4)	8.2	(2.8)	<.001 ^{a,b}
Current income (Rands per week)—mean (SD)	421.5	(283.8)	698.9	(758.4)	772.8	(780.0)	.008 ^b

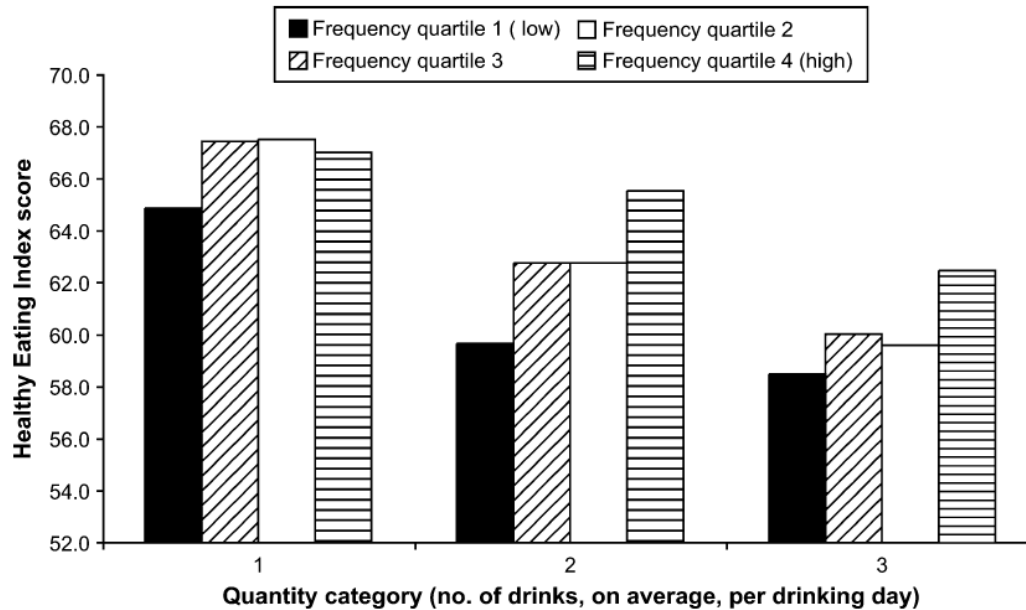
Maternal nutritional status as a contributing factor for the risk of fetal alcohol spectrum disorders

Philip A. May^{a,b,*}, Kari J. Hamrick^c, Karen D. Corbin^d, Julie M. Hasken^a, Anna-Susan Marais^{e,f}, Jason Blankenship^b, H. Eugene Hoyme^g, J. Phillip Gossage^b



How does diet change across the population based on alcohol intake?

- A 2005 analysis in the USA demonstrated that as the quality of diet increased within the population, so did the frequency of alcohol consumption
- When this was reanalysed based on drinks within a single day, the opposite was true
- The quality of food intake was found to decrease as the number of drinks in a single occasion increased



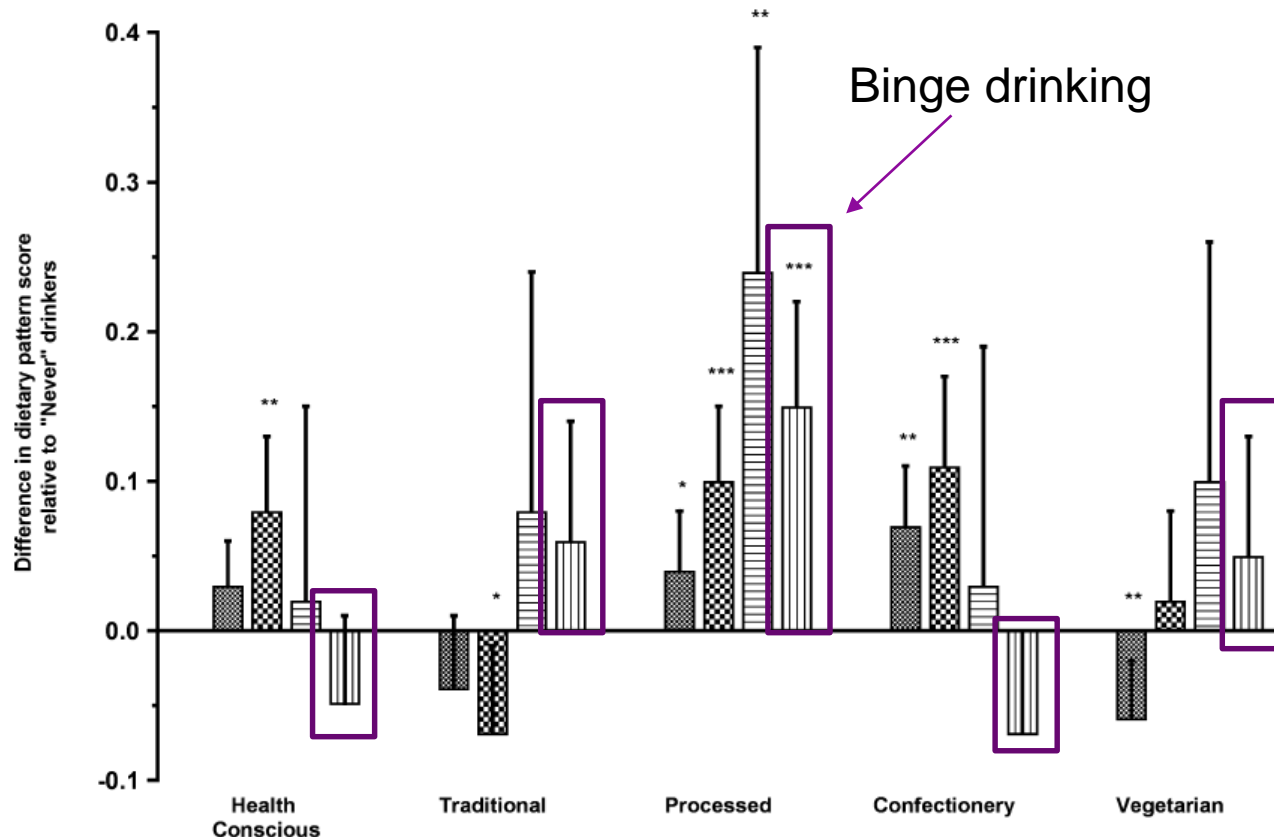
Poor diet is more strongly associated with Binge drinking

Alcohol Drinking Patterns and Diet Quality: The 1999–2000 National Health and Nutrition Examination Survey. Rosalind et al, American Journal of Epidemiology



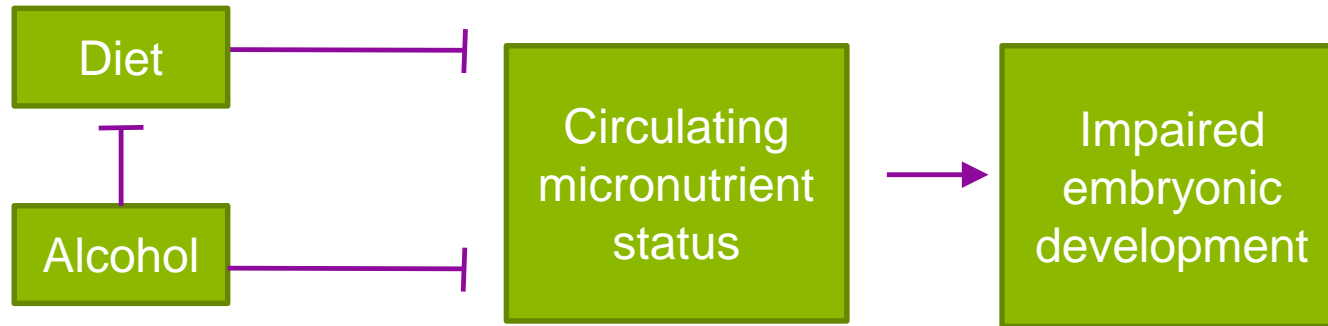
Behaviors linking Alcohol consumption and food quality in pregnancy

- Low level alcohol consumption may be associated with health conscious diets
- Binge drinking in pregnancy associated with consumption of highly processed foods



Coathup 2017

Alcohol intake and micronutrients



Minerals

- **Alcohol reduces selenium**
- **Alcohol reduces zinc content**
- Iron seems to be increased by alcohol
- Uptake of other trace elements may also be impaired

Nutrition Implications for Fetal Alcohol Spectrum Disorder,

Young et al, American Society of Nutrition 5: 675, 2014

Effect of Alcohol Consumption on the Gut

Rajkumar Rajendram and Victor R. Preedy, Dig Dis 2005;23:214–221

Alcohol can impair the ability of the body to absorb micronutrients

Vitamins

- Folate absorption impaired
- **Choline absorption impaired**
- Impaired riboflavin (B2)
- **Impaired Vitamin B12 absorption**
- Reduces Thiamine absorption
- Does not affect fat soluble vitamin absorption (Vitamin A, D, E and K)
- But reduces their concentrations through other processes

Nutrition Implications for Fetal Alcohol Spectrum Disorder,

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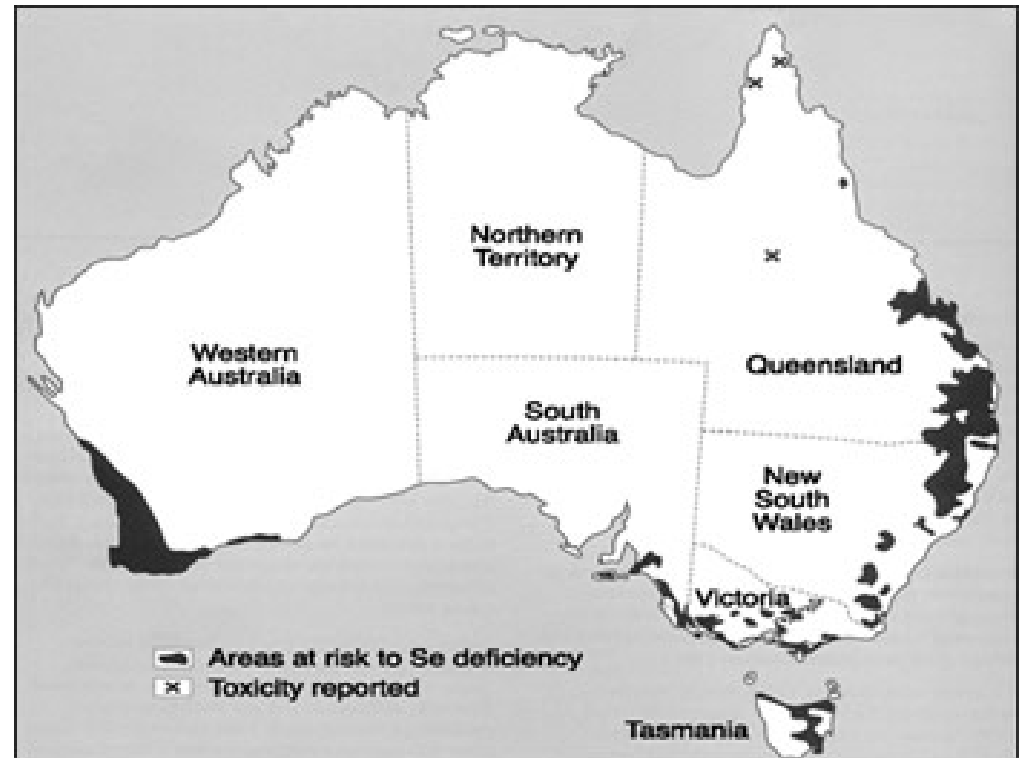
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Why are so many women deficient in micronutrients?

- If we are eating a healthy diet surely we should have appropriate micronutrient status?
- Mineral content in the food chain (Fruit, vegetables, meat) reflect concentrations found in soil
- In areas of over farming and high population density, mineral content in food is likely to be low.

Areas at risk of selenium deficiency

Plasma selenium content reduced in a cohort of Gold Coast women in pregnancy (2018 unpublished data, Griffith University)

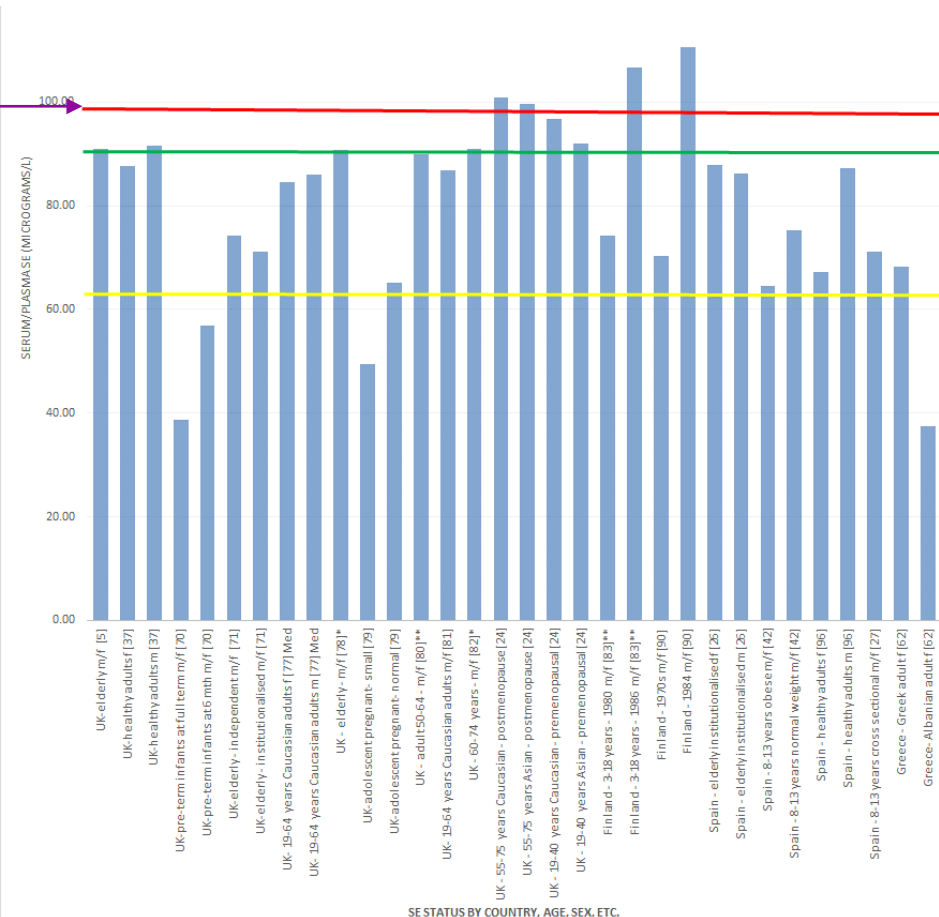


How do these low levels in soil reflect blood concentrations required for health

- Do we have enough selenium in our blood for us to be healthy?

Level required for optimal health

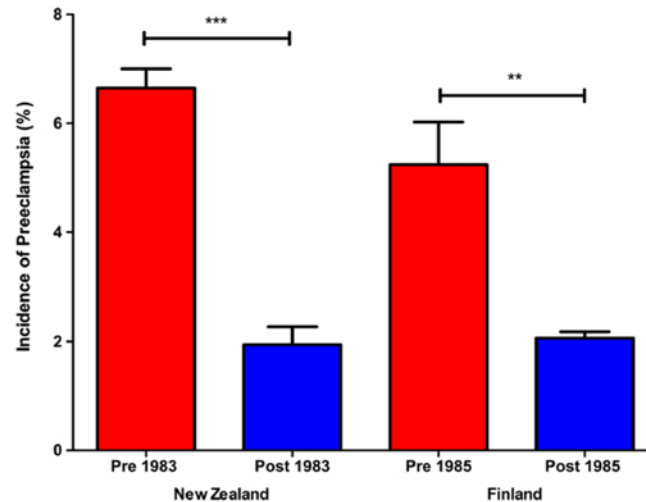
Most European nations are selenium deficient



Impact of low selenium on pregnancy health?

- Selenium deficiency increases risk of preeclampsia, thyroid dysfunction, gestational diabetes
- Selenium intake is perturbed by alcohol consumption

Selenium fortification reduces PE



Vanderlelie and Perkins 2011



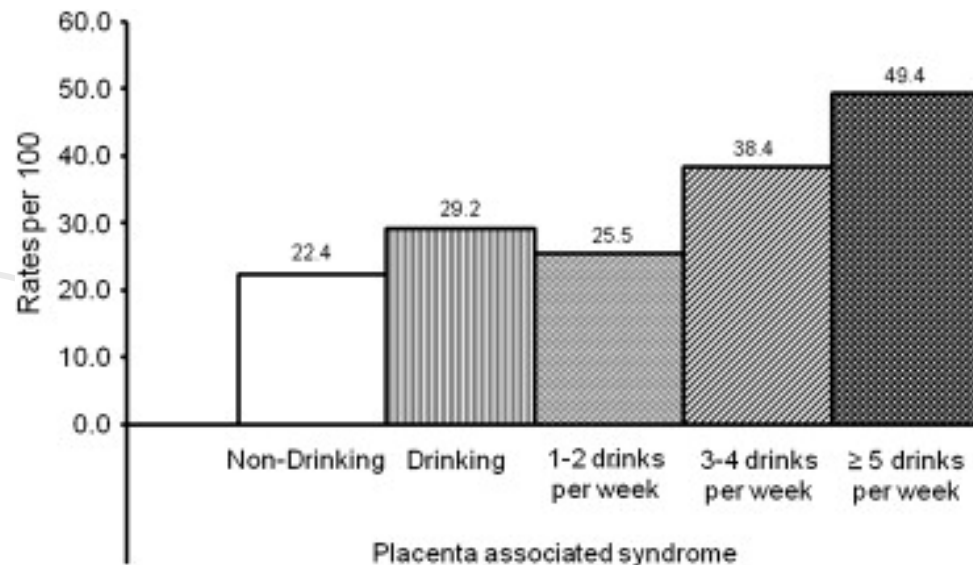
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Alcohol exposure can impair function of selenium dependant proteins leading to oxidative stress

Maternal ethanol consumption reduces Se antioxidant function in placenta and liver of embryos and breastfeeding pups

Fátima Nogales^{a,1}, M. Luisa Ojeda^{a,1}, Karick Jotty^b, M. Luisa Murillo^a, Olimpia Carreras^{a,*}



Impact of prenatal alcohol consumption on placenta-associated syndromes

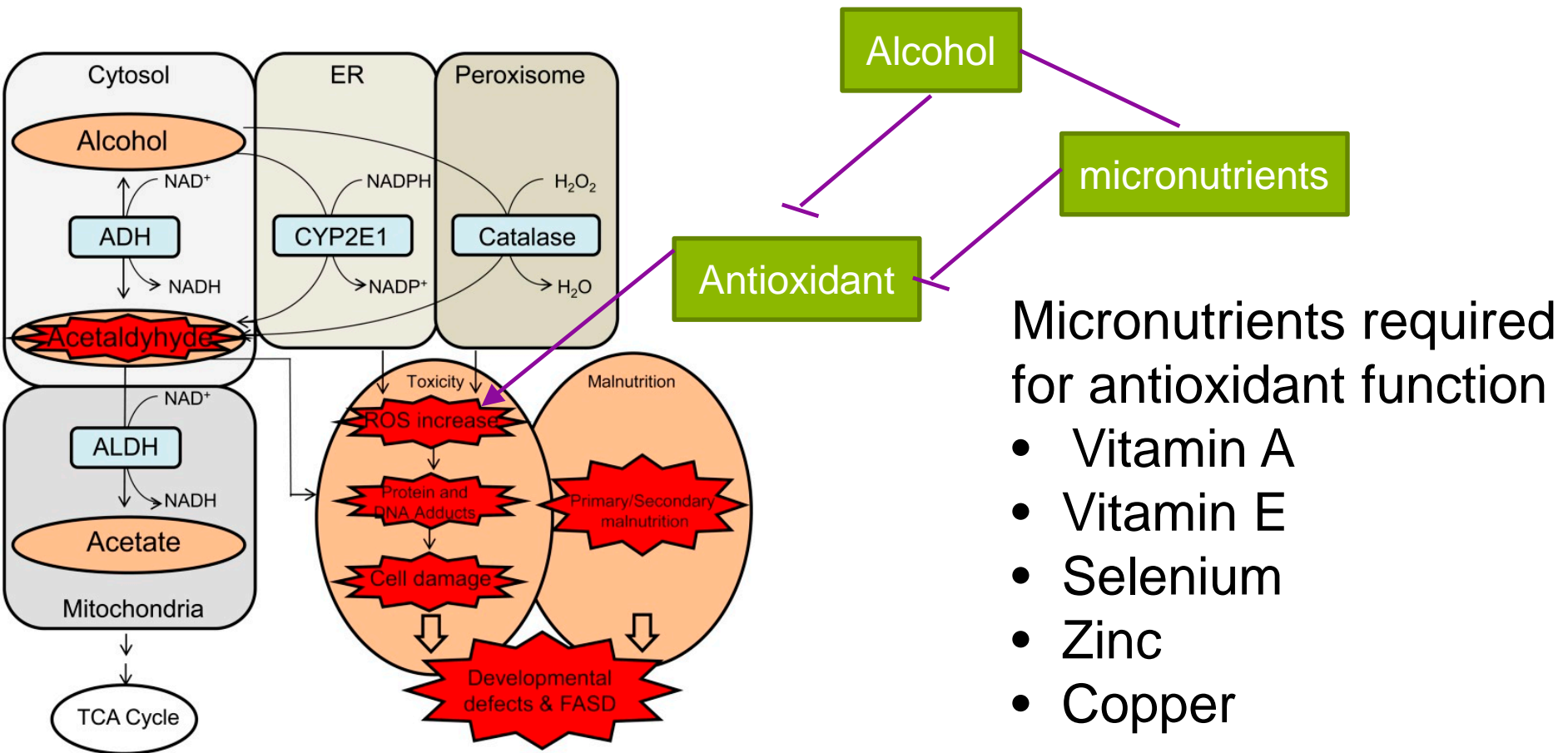
Hamisu M. Salihu^{a,b,c,*}, Jennifer L. Kornosky^b, O'Neil Lynch^d, Amina P. Alio^e, Euna M. August^{a,e}, Phillip J. Marty^a



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What biological processes that are impacted by ethanol in pregnancy may be exacerbated by impaired nutrition?



What biological processes that are impacted by ethanol in pregnancy may be exacerbated by impaired nutrition?

Endocrine disorders (eg thyroid hormone)

Alcohol

Selenium and
Iodine uptake

Thyroid Function in Pregnant Women With Moderate to Severe Alcohol Consumption Is Related to Infant Developmental Outcomes

Kirsten A. Donald^{1}, Catherine J. Wedderburn^{1,2}, Whitney Barnett^{3,4}, Nadia Hoffman⁵, Heather J. Zar^{3,4}, Eva E. Redei^{6,7†} and Dan J. Stein^{5,8†}*

Thyroid hormone
(T3/T4) production
(or other hormones)

Exacerbates
neurological outcomes
associated with FASD

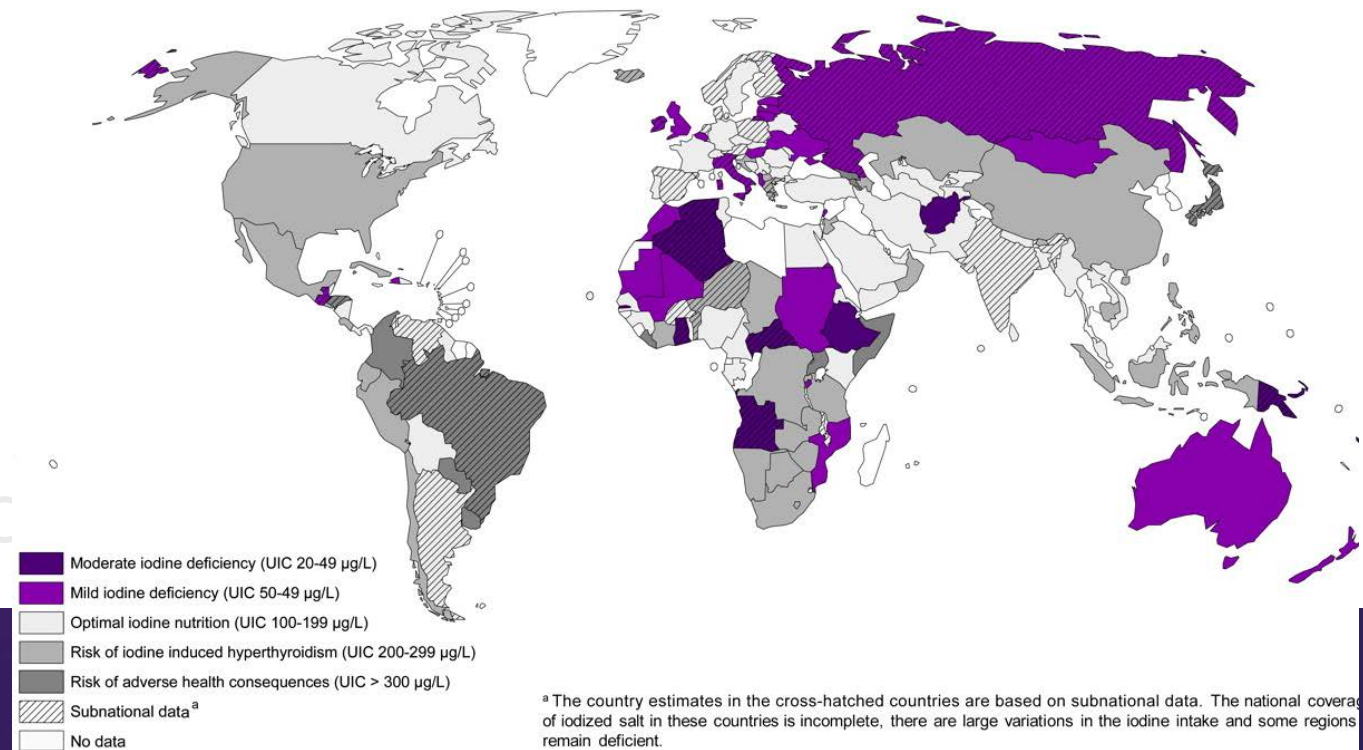


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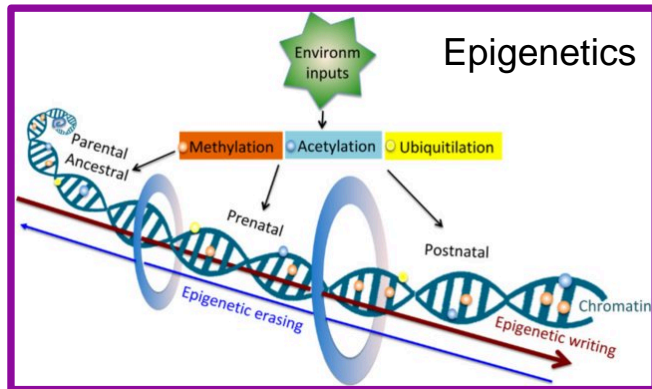
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Iodine deficiency


- Alcohol consumption increases iodine excretion population
- Iodine is most famously known for being important for thyroid hormone
- Alcohol and iodine deficiency may synergistically impair brain development
- Perkins Lab have shown in a small study that pregnant women from Gold Coast are low in Iodine



What biological processes that are impacted by ethanol may be as an indirect consequence of impaired nutrition?



Effect of Choline Supplementation on Neurological, Cognitive, and Behavioral Outcomes in Offspring Arising from Alcohol Exposure During Development: A Quantitative Systematic Review of Clinical and Preclinical Studies

Lisa K. Akison , Jenny Kuo, Natasha Reid , Roslyn N. Boyd, and Karen M. Moritz

Alcohol

Choline,
Folate, B Vits

Epigenetic
processes

Exacerbates
neurological outcomes
associated with FASD



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Can we use nutrition or micronutrient supplementation to intervene to reduce risk of FASD or minimise severity of outcomes?

Iodine
supplement

Low-Dose Thyroxine Attenuates Autism-Associated Adverse Effects of Fetal Alcohol in Male Offspring's Social Behavior and Hippocampal Gene Expression

Elif Tunc-Ozcan*, Timothy M. Ullmann*, Pradeep K. Shukla, and Eva E. Redei

Choline
supplement

Effect of Choline Supplementation on Neurological, Cognitive, and Behavioral Outcomes in Offspring Arising from Alcohol Exposure During Development: A Quantitative Systematic Review of Clinical and Preclinical Studies

Lisa K. Akison , Jenny Kuo, Natasha Reid , Roslyn N. Boyd, and Karen M. Moritz

Selenium
supplement

The role of folic acid and selenium against oxidative damage from ethanol in early life programming: a review¹

Luisa Ojeda, Fátima Nogales, Luisa Murillo, and Olimpia Carreras



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Choline supplementation in rat model improves fetal growth impaired by alcohol exposure

Preliminary evidence that mid-gestational choline supplementation in a rat model increases birth weight (2018 Unpublished data, University of Queensland)



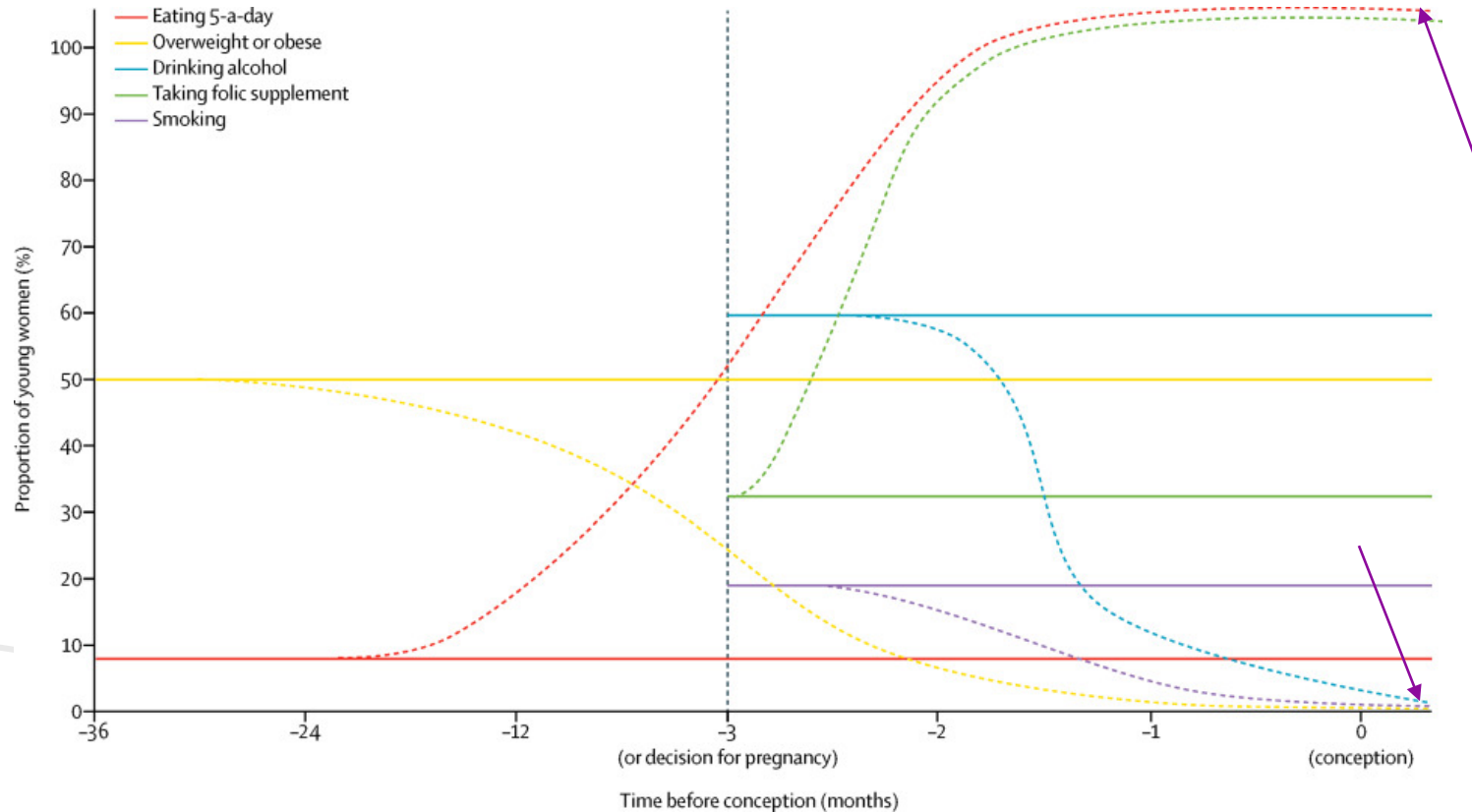
When might be a good time to supplement/modify diet to improve outcomes for children?

- Should we be focusing on improving population level nutrition?
- Should we be focusing on diet and supplementation in ?
- Should this be different in women who do and do not consume alcohol?
- Should we be focusing on improving nutrition for children with FASD instead?

Should we all simply supplement everyone with all required micronutrients?

- Currently guidelines simply state: Eat a healthy diet and supplement with folate and iodine (maybe Iron)
- Others micronutrient supplements required in some women
- More research is needed in this space to determine benefit of supplementation
- However supplementation may prove to be the simplest intervention to minimise poor outcomes
- Current priority should be to increase awareness of importance of eating appropriately

The challenge for improving childhood outcomes



Typical levels of each preconception behaviour in young women in high-income countries (solid lines) and optimal behaviours before conception (dashed lines).





Where to from here?





FASD: Prevention is key BUT need education and interventions

- Prevalence is likely to be higher than earlier estimates– most children are not diagnosed
- Exposure to alcohol can result in a range of developmental issues and potential long term health consequences.
- Preventable
- Education of health professionals and society required





Research: a wise investment

“The global effort to improve child health begins with research.there is a critical need to invest in further research to build on the advances already in place. Without such an investment, the larger goal before us - to significantly reduce the global burden of disease - may never again be so attainable.”

World Health Organisation





FASD – a time for action!

Face facts

Act all stages

Stop stigma

Discuss and diagnose

Useful link: <https://www.nofasd.org.au/>

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