Fetal Alcohol Canadian Expertise
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The Association between FAEE in Meconium and the Diagnosis of FASD in an at-risk Canadian Population

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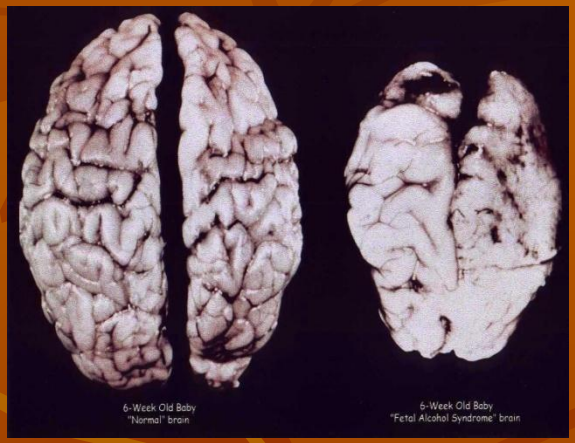
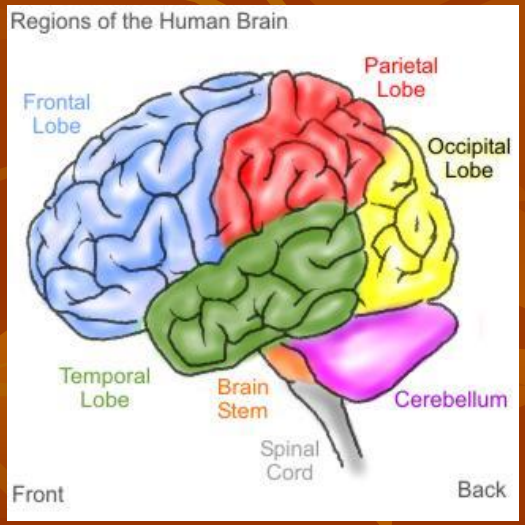
This study aims to evaluate the ability of a prenatal alcohol exposure biomarker (meconium fatty acid ethyl esters) to predict a diagnosis of FASD

Effects of Prenatal Ethanol

- Effects on brain development (Jones and Smith, 1973; Clarren, 1986; Mattson and Riley, 1996; Sowell et al., 2001; Green et al., 2005; Riley and McGee, 2005)
  - overall reductions in brain size
  - abnormalities in brain shape
  - altered expression of gray and white matter
  - severe hypotrophy of the corpus callosum
  - hippocampus, cerebellum, brainstem, frontal lobe, temporal lobe, parietal lobe, and basal ganglia

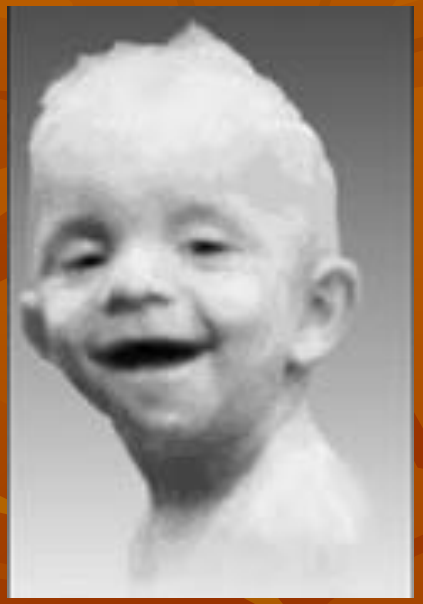


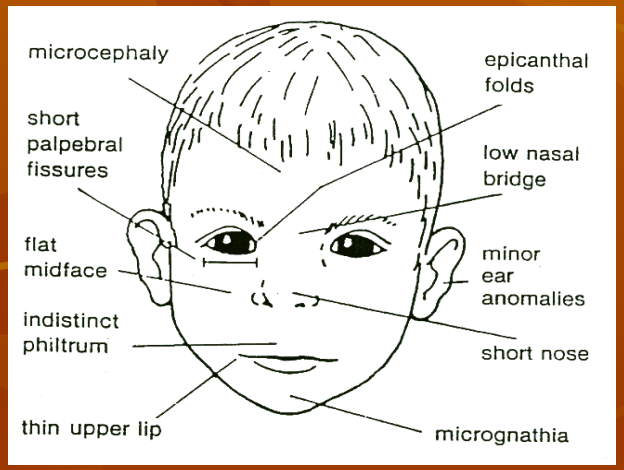
- Widespread effects on brain signalling systems (Iqbal et al., 2005; Carneiro et al., 2005; Galindo et al., 2005)
  - Glucorticoid
  - Glutamatergic
  - dopaminergic,
  - Muscarinic
  - GABAergic signaling systems in FASD animal models



Effects of Prenatal Ethanol

- Deficits (Riley and McGee, 2005)
  - Acquisition of information/comprehension
  - Visual attention/shifting attention
  - Cognitive flexibility, response inhibition
  - Planning, concept formation, reasoning





- "The true challenge with FASD is that while not all patients display the physical features of the disease, **all** show deficits in several areas of neurobehavioural functioning" (Mattson and Riley, 1998)

Benefits of Early Intervention

- Intervention **prior to age 6** is optimal
  - Significant attenuation of secondary disabilities

- Secondary Disabilities (Streissguth *et al.* 1996, Olsen *et al.* 1997)
  - "disrupted school experience" and "trouble with the law"
  - institutionalization/incarceration
  - unemployment/ dependent living
  - inappropriate or promiscuous sexual behaviour
  - mental health problems/substance addiction

- Early intervention is rare

- Methods of early screening are needed

Importance of Exposure History

(Chudley *et al.* 2005)

A. Presence of the 3 characteristic facial features (short palpebral fissures, smooth or flattened philtrum, thin vermilion border).
B. ***Evidence of significant prenatal exposure to alcohol*** at levels known to be associated with physical or developmental effects, or both.
C. Presence of 1 or more facial features with growth deficits ***plus known or probable significant prenatal alcohol exposure.***
D. Presence of 1 or more facial features with 1 or more central nervous system deficits ***plus known or probable significant prenatal alcohol exposure.***
E. Presence of 1 or more facial features with pre- or postnatal growth deficits or both (at the 10th percentile or below [1.5 SD below the mean]) and 1 or more central nervous system deficits ***plus known or probable significant prenatal alcohol exposure.***

Early Intervention

- Points of contact for intervention
  - Birth/delivery
    - Evidence of prenatal alcohol exposure
  - School
    - Behavioural issues
  - Social Services
    - History of prenatal alcohol exposure
    - Behavioural issues
  - Justice System
    - Behavioural issues

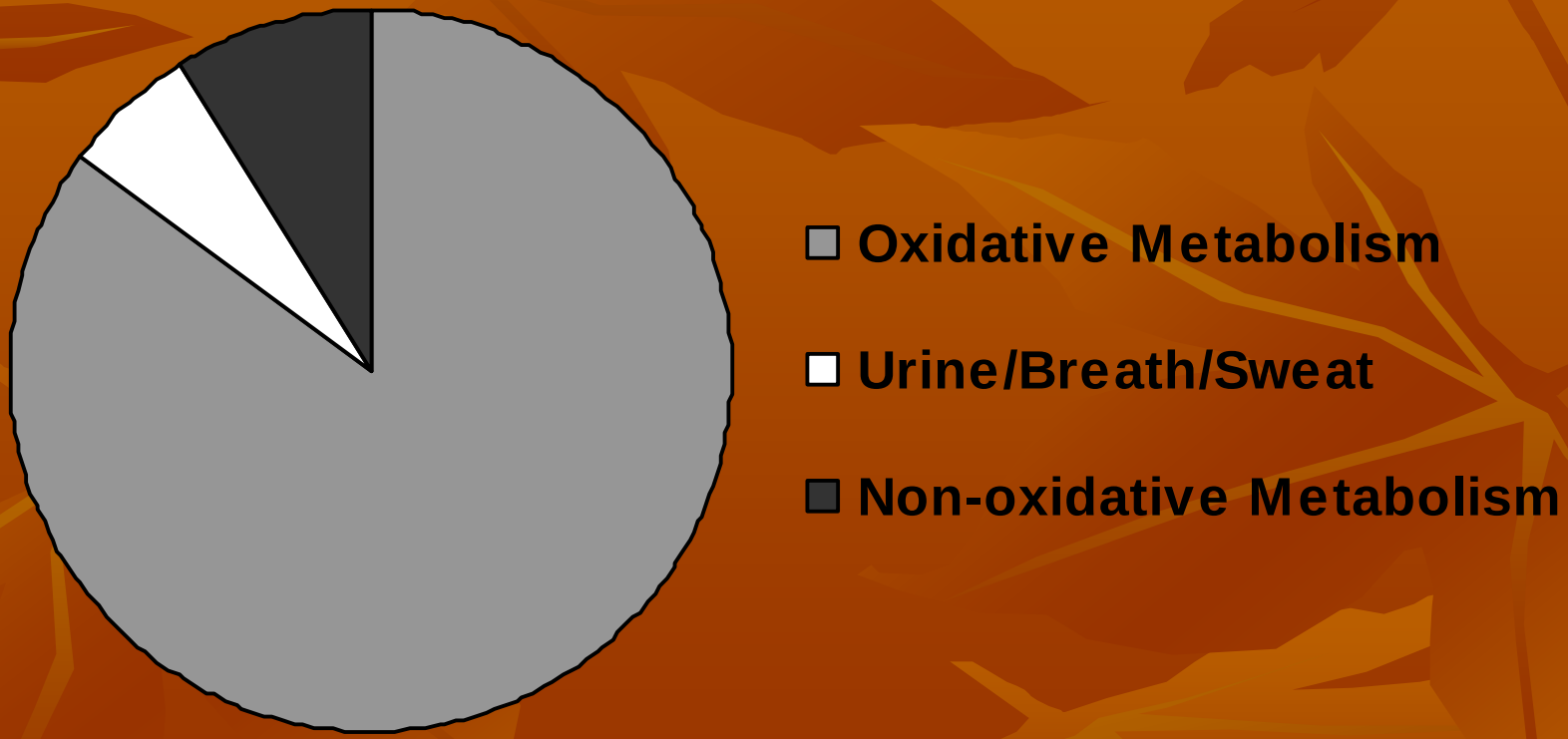
Determining Prenatal Alcohol Exposure

- Traditional maternal biomarkers of alcoholism ineffective in pregnancy
- Stigma of alcohol/drug abuse in pregnancy
- Marginalization & blame
- Shame, guilt, fear of punishment
- Lack of established trust with researcher/ physician

↓↓↓ sensitivity of self-reporting measures

- Stoler *et al.* Journal of Pediatrics 1998; 133: 346-352
- Russell *et al.* American Journal of Public Health 1996; 86: 1435-1439.
- Neumann T, Spies C. Addiction 2003; 98(2): 81-91.

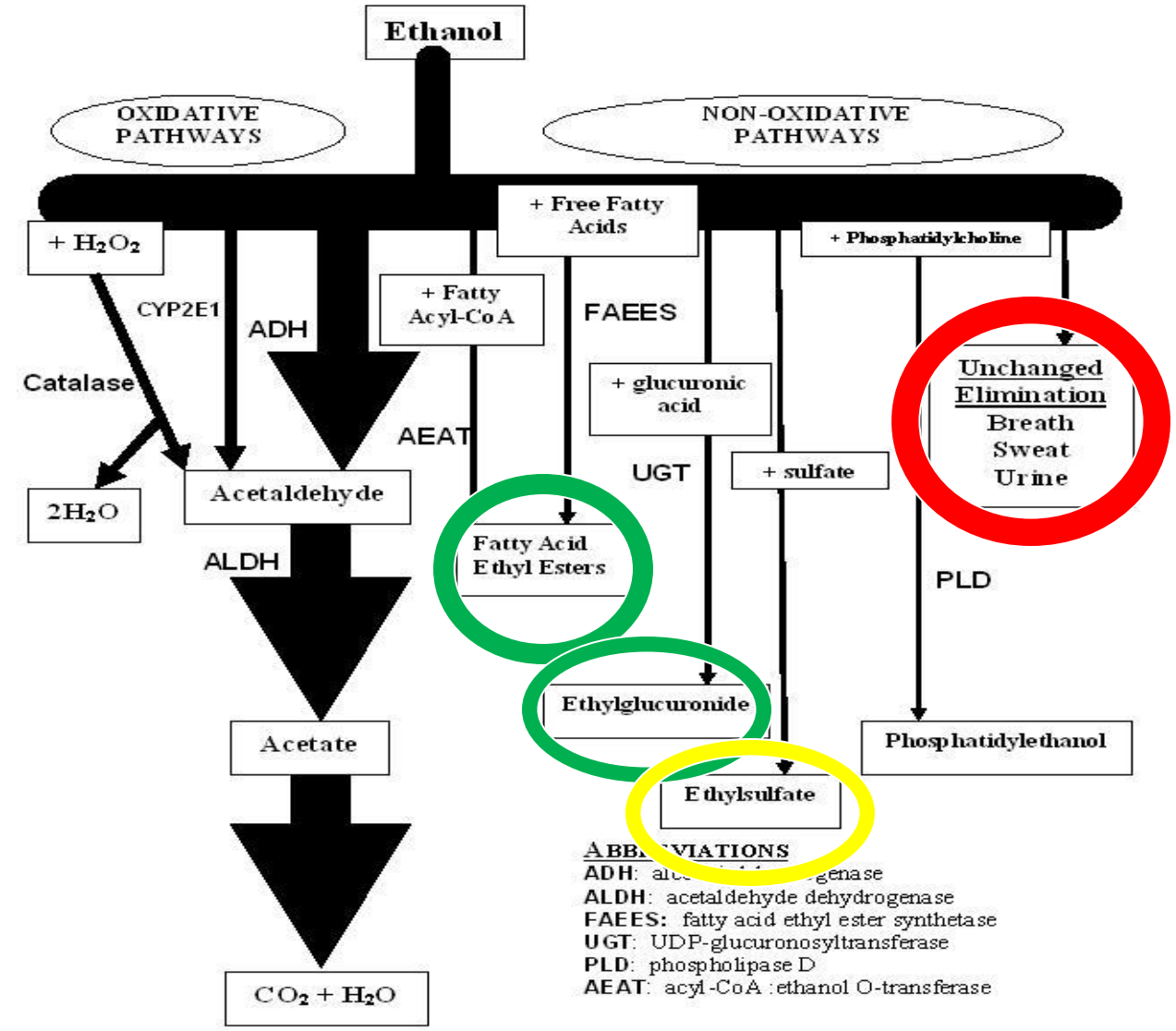
Ethanol Metabolism & Elimination



Detecting Alcohol Abuse

- One standard drink *(Canadian definition)*
  - 13.6 grams of ethanol
    - 12 oz. beer (5%)
    - 5 oz. wine (12-15%)
    - 1.5 oz. liquor (40%)
- Alcohol Elimination Rate: ~7 g per hour
  - e.g. 5 drinks in 1 hour (i.e. binge episode)
    - 0 BAC within 10 hours
    - 0 UAC within 12 hours

FIGURE 1.2: PATHWAYS OF ETHANOL METABOLISM
(Kalant and Khanna, 1998; Swift, 2003; Best and Laposata, 2003)



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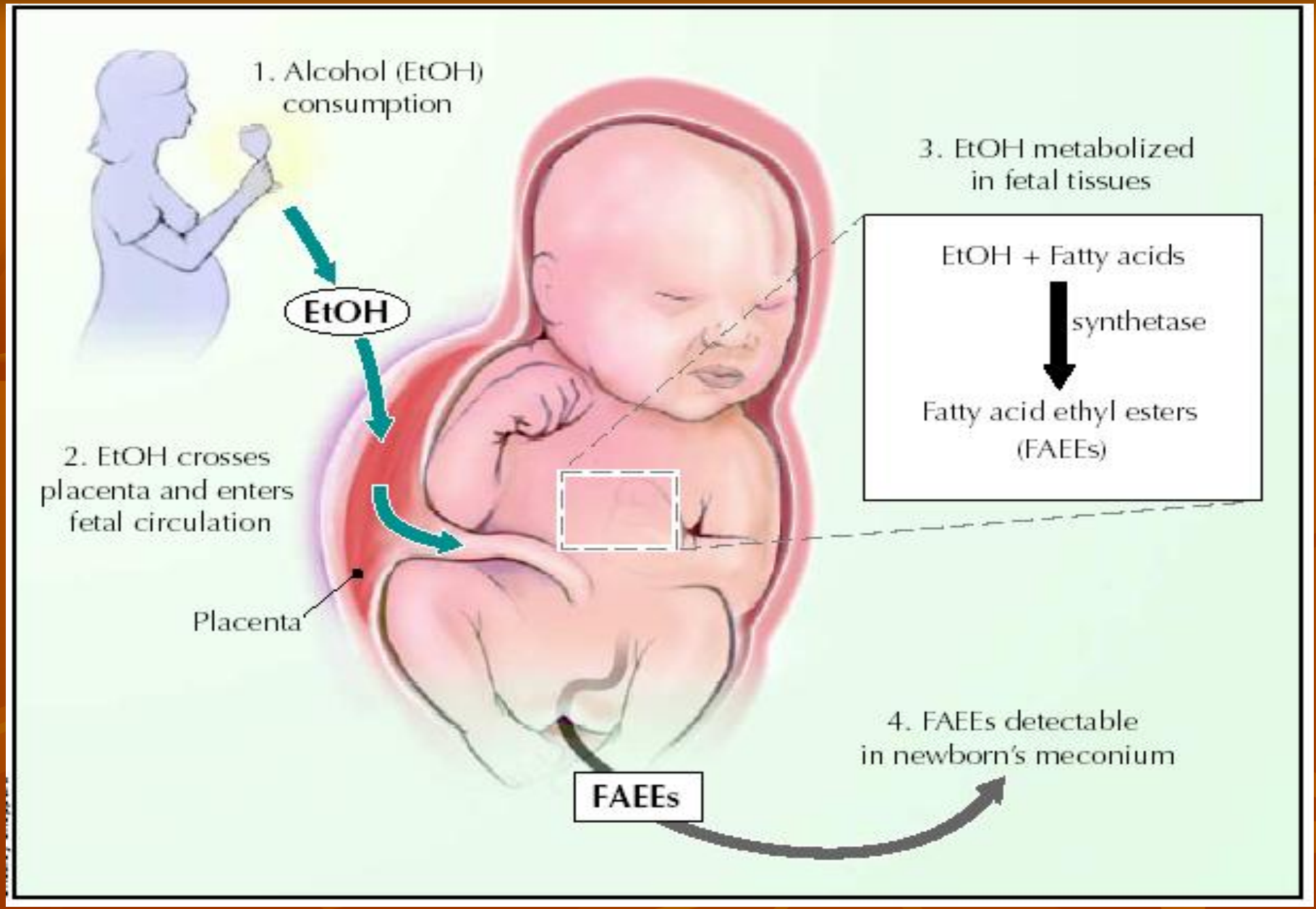

Koren *et al*. *CMAJ* 2003;169:1181-5.

Background: Meconium

- Complex matrix
  - Water, epithelial cells, lanugo, bile acids and salts, blood group substances, enzymes, mucopolysaccharides, lipids, proteins, trace metals, etc.
- Timing of Formation
  - ~12 weeks of gestation
  - Coincident with initiation of fetal swallowing
- Some advantages over blood and urine
  - Discarded material
  - Collection is easy and non-invasive

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- Kwong TC, Ryan RM. Clin Chem 1997;43:235– 42.
- Browne SP *et al*. J Chromatogr 1992;575:158– 61.
- Vaughan V, Litt I. Nelson textbook of pediatrics. 13th ed. Philadelphia' Saunders; 1987.

Background: FAEE meconium & alcohol exposure

- **Bearer *et al.* 1999, Klein *et al.* 1999**
  - Correlation with gestational ethanol consumption
  - Ethyl linolate; ≥ 1 drink/week (N = 248)
- **Bearer *et al.* 2003**
  - Ethyl oleate; ≥ 1.5 oz. ethanol/drinking day (N = 27)
- **Chan *et al.* 2003**
  - **Positive cut-off = 2.0 nmol/g cumulative [FAEE]**
- **Chan *et al.* 2004**
  - FAEE do not cross placenta
- **Brien *et al.* 2006**
  - Negative correlation between meconium [FAEE] and fetal brain weight in guinea pigs

Background: FAEE meconium & outcomes

- **Derauf *et al.* 2003**
  - Lower one-minute Apgar scores ($p = 0.003$); low birth weight ($p = 0.006$)
- **Noland *et al.* 2003**
  - Decreased score on executive functioning task
  - Lower birth weight, length, head circumference
- **Peterson *et al.* 2005**
  - Decreased psychomotor performance (age 2 years; $P < 0.04$)
- **Jacobson *et al.* 2006**
  - Correlation with FAS or pFAS diagnosis (age 5 years; $p < 0.005$)
  - [ethyl oleate] > maternal self-report correlates to:
    - Recognition memory, Processing speed, Complexity of symbolic play
- **Peterson *et al.* 2008**
  - Poor mental and psychomotor development (6.5 months – 2 years; $p < 0.05$)

STUDY RATIONALE

- early intervention is key to improving FASD outcomes
- early identification carries significant challenges regarding self-report reliability and routinely available analytical methods
- FAEE in meconium is a long-term biomarker of prenatal exposure history and potential FASD outcomes
- **Is FAEE a reliable screening tool in predicting FASD diagnosis?**

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- Objective
  - To assess FAEE meconium-positive children for neurodevelopmental impairments associated with FASD

- Hypotheses
  - Meconium FAEE levels greater than or equal to 2 nmol cumulative FAEE per gram of meconium will significantly predict a diagnosis of FASD

  - Higher meconium FAEE levels will predict a greater severity of neurodevelopmental deficits

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- Study Design
  - Case-control cohort study using a prospectively analyzed meconium results database
  - Subjects
    - Children tested for meconium FAEE based on suspicion of gestational alcohol exposure since 1997
    - Positive meconium results for FAEE greater than or equal to 2 nmol/g
    - Children $\geq$ 3 years of age

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- Control Subjects
  - Children tested for meconium FAEE based on suspicion of gestational alcohol exposure since 1997
  - Negative meconium FAEE results (< 2 nmol/g)
- Matching Criteria
  - Age, gender
  - Other drug exposures evidenced through meconium analysis (e.g. cocaine, cannabis, etc.)
  - Number of placements in foster homes (+/- 2).

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- Sample Size
  - 462 eligible samples (Toronto area / FAEE-tested)
  - 64 positive FAEE results (≥ 2 nmol/g)
  - Recruitment Estimate ~50%
  - **Predicted sample size N = 64**
    - n = 32 case subjects
    - n = 32 matched controls

- Measures
  - FASD Diagnosis via Motherisk FASD Clinic, Hospital for Sick Children
  - Physical assessment
  - Standard battery of diagnostic tests adhering to the Canadian FASD Guidelines (Chudley et al., 2005).
  - Post-assessment, clinic physicians and psychologists will apply the FASD diagnostic criteria and accept or reject a diagnosis of FASD pending exposure status.

Study Recruitment

- **PHASE I**
  - The social worker or healthcare provider that requested the meconium test was sent a letter outlining the purpose of the study and requesting permission to contact the guardian of the child. The letter does not include the result of the meconium test for FAEE.

- **PHASE II**
  - If permission to contact the child's guardian is granted; contact information is obtained and a letter is forwarded requesting enrollment in the study.
  - Letters are followed up by telephone calls
  - Verbal consent to enroll in the study is followed by written informed consent to participate upon clinic attendance

Results: Recruitment Phase I

- **N = 64** children identified with positive meconium FAEE findings born between January 1998 and June 2007
  - Phase I recruitment letters were sent out to social workers, physicians and hospitals requesting permission to contact the families of these children in January 2010

- Preliminary Study Recruitment Data
  - **n = 1** child deceased (accidental death at 1 y.o.)
  - **n = 6** received permission to contact families and were provided with some form of contact information
  - **n = 6** received permission to contact families but were provided with no contact information / no contact information available. Communication with point of contact ongoing
  - **n = 3** point of contact has no information / record regarding child in question

Results: Recruitment Phase II

- **n = 2** children enrolled in study
  - Guardians referred directly by initial contact person and provided consent
  - Both children adopted
  - Scheduled to attend Hospital for Sick Children for FASD assessment in October 2010

- **n = 6** guardians to receive recruitment letter
  - Some form of potentially viable contact information for family has been obtained from primary contact

Future Directions: Recruitment Phase I

- n = 24 children with FAEE-positive meconium results identified are eligible for recruitment
  - Phase I recruitment letters to be issued **January 2011**
- n = 24 children with FAEE-positive meconium results identified will be eligible for recruitment in July 2011
  - Phase I recruitment letters to be issued **July 2011**
- n = 30 children with FAEE-positive meconium results identified will be eligible for recruitment in January 2012
  - Phase I recruitment letters to be issued **January 2012**

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- Timeline
  - Continued recruitment of subjects: Fall 2010 through Spring 2012
  - Recruitment of controls to begin after 1st subjects seen in clinic
  - FASD assessments: 2010 – 2012
  - Data interpretation / Manuscript preparation: Summer/Fall 2012

THANK YOU ☺

THE END

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