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Meconium Alcohol and Drug Screening

by

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Meconium Alcohol and Drug Screening " submitted by Matthew Stephen Hicks in partial fulfilment of the requirements of the degree of Doctor of Philosophy.

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Abstract

Screening of meconium for fatty acid ethyl esters (FAEEs), ethanol metabolites produced by the fetus which accumulate in meconium in the last half of pregnancy, has been proposed to identify infants at risk of deficits associated with prenatal alcohol exposure. In this study the association between meconium FAEEs and 1) maternal alcohol use, and 2) child development at 2-years of age was examined. Women's willingness to consent to screening of their infants was also explored.

A prospective population-based cohort study of women attending Calgary maternity clinics was conducted 2002-2005. Participants completed 3 perinatal questionnaires including questions about lifestyle and psychosocial factors. Meconium was collected and analyzed for FAEEs. At 2-years of age child development was assessed by Bayley Scales of Infant Development (BSID-II), paediatrician and standardized questionnaires. In addition, a cross-sectional survey examining willingness to consent to screening was administered on postpartum units.

Of eligible women, 344/460 (75%) participated with a sample collection rate of 238/344 (70%). There was no association between maternal report of alcohol use and FAEE concentration. Infants born to women who reported alcohol use did not have elevated FAEEs. Male infants were more likely to have meconium positive for FAEEs. At 2-years of age (75% follow up rate), FAEE concentration was correlated (rho -0.2045, p value 0.027) with BSID-II Psychomotor Development Index (PDI). In regression analyses FAEE $\geq$ 5,000 ng/g was associated with motor delay (AOR 26.92, 95%CI 3.36-215.47) and a decrease of 8.8 points (95% CI -16.9 to -0.6) on BSID-II PDI.

The cross-sectional willingness to consent survey was administered to 1509 mothers (78.4% participation rate). Mothers would consent to screening of their newborns (1369/1460, 93.8%), and thought women should consent if infants received effective treatment (1440/1476, 97.6%). In regression analysis, belief that universal screening would reduce discrimination was a predictor of consent, (AOR 5.9, 95%CI 3.3-10.6). Women would support a universal screen if there was evidence of effective treatment.

Further research is required to understand the factors that modify FAEE production, whether motor delays persist as these children age, and whether interventions for children identified at birth with high meconium FAEE concentrations are effective.

Preface

The Meconium Alcohol and Drug Screening (MEC) Study was initiated based on increasing interest at a regional and national level in exploring methods for early identification of children at risk for developmental delay as a consequence of prenatal alcohol and drug exposure. Currently, children are often not diagnosed until late childhood and the opportunity for early interventions which could improve the life course of these children is delayed or missed. In addition to the family and caregiver's stress associated with caring for a child with an undiagnosed disability, the consequences of late diagnosis and late intervention include increased risks of school failure, unemployment, and trouble with the law. There is a tremendous cost to society associated with caring for individuals with a Fetal Alcohol Spectrum Disorder (FASD). Early identification holds promise for earlier intervention, improved outcomes and decreased family and societal costs.

This thesis examines 3 fundamental questions related to alcohol and drug biomarker screening:

- Is maternal report of alcohol use associated with elevated concentration of a biomarker?;
- Is elevated concentration of biomarker associated with deficits or delay in child development?; and
- Under what conditions would mothers consent to drug and alcohol screening of their newborns?

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Dedication

To

My Mother

Mary-Lynn Hicks

and

My Wife

Elizabeth Anne Hicks

Thank you.

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List of Symbols, Abbreviations and Nomenclature

Symbol/Abbreviation	Definition
ABAS	Adaptive Behavior Assessment System
ACH	Alberta Children's Hospital
ADH	Alcohol dehydrogenase, a main enzyme in the metabolism of alcohol to acetaldehyde
ALDH	Aldehyde hydrogenase, the enyzme that converts acetaldehyde to acetate
AOR	Adjusted Odds Ratio
ARBD	Alcohol-related Birth Defects
ARND	Alcohol-related Neuorodevelopmental Disorder
AUDIT	Screening tool for alcohol dependence/risk drinking
BSID-II	Bayley Scales of Infant Development, 2nd edition
CAGE	Screening tool for alcohol dependence/risk drinking
CATI	Computer Assisted Telephone Interviewing
CBCL	Child Behavior Checklist
CHR	Calgary Health Region
CNS	Central Nervous System
CPC Study	Community Perinatal Care Study
CUPS	Calgary Urban Projects Society
FAD	McMaster Family Assessment Device
FAE	Fetal Alcohol Effects
FAEEs	Fatty Acid Ethyl Esters
FAS	Fetal Alcohol Syndrome
FASD	Fetal Alcohol Spectrum Disorders
4-Digit Diagnostic Criteria	Diagnostic approach to standardize the diagnosis of FAS
HSQ	Home Screening Questionnaire
IOM Diagnostic Criteria	Institute of Medicine Diagnostic Criteria for FAS; Hoyme’s Criteria
MDI	Bayley Scales of Infant Development, 2nd edition Mental Development Index
MEC Study	Meconium Alcohol and Drug Screening Study
NDDS	Nippissing District Developmental Screener
Partial FAS	Partial Fetal Alcohol Syndrome
PCP	Phencyclidine
PDI	Bayley Scales of Infant Development, 2nd edition Psychomotor Development Index
PSS	Parenting Satisfaction Scale
SES	Socio-economic status
SPSS	Statistical Packages for the Social Sciences

TABS	Temperament and Adaptive Behavior Scale
T-ACE	Screening tool for alcohol dependence/risk drinking
TTS	Toddler Temperament Scale
TWEAK	Screening tool for alcohol dependence/risk drinking
USDTL	United States Drug Tests Labs Inc
WASI	Wechsler Abbreviated Scale of Intelligence
WHO	World Health Organization

Epigraph

The same thrill, the same awe and mystery, comes again and again when we look at any question deeply enough. With more knowledge comes a deeper, more wonderful mystery, luring one on to penetrate deeper still. Never concerned that the answer may prove disappointing, with pleasure and confidence we turn over each new stone to find unimagined strangeness leading on to more wonderful questions and mysteries - certainly a grand adventure!

Richard Feynman ,*The Value of Science*, 1955

Chapter One: Introduction

1.1 Background

The deficits associated with prenatal alcohol exposure are believed to represent the most common non-genetic cause of mental, learning and behavioral disabilities in North America and are serious lifelong conditions (1-5). The disabilities include diagnoses captured by Fetal Alcohol Spectrum Disorder (FASD); including Fetal Alcohol Syndrome (FAS), Partial FAS, Alcohol-related Birth Defects (ARBD), and Alcohol-related Neurodevelopmental Disorder (ARND) (6). There are also deficits in motor and mental development associated with prenatal alcohol exposure that do not meet the diagnostic criteria for an FASD. The reported conservative estimates of the prevalence of FAS/FASD for urban North American populations is 0.23 to 3 cases per 1,000 live births for FAS, and approximately 9.1 per 1,000 live births for FASD (7-12). The reported prevalence in rural communities, foster care systems and juvenile justice systems can be much higher with rates of 7.2 to 233/1,000 found in high risk populations in Manitoba and British Columbia while rates of 39.3 to 98.0/1,000 live births have been reported in rural South Africa (13-17). Most recently a case-finding study in Italian urban schools found a prevalence for FAS of 3.7 to 7.4 per 1,000 children and a prevalence of FASD of 20.3 to 40.5 per 1,000 children (18). Combining alcohol use with the use of other substances like cannabis (e.g., marijuana), opiates (e.g., heroin, morphine, and methadone), amphetamines (e.g., speed), phencyclidine (e.g., PCP, and angel dust) and cocaine (e.g., crack) may produce a confusing array of effects on the developing fetus (19). Prenatal drug exposure can result in permanent health problems including developmental delay (20;21).

Primary disabilities of FASD include growth deficiencies, major organ malformation, vision and hearing problems, cognitive, motor, behavioral and psychosocial problems (22-35). Secondary disabilities that arise as a consequence of the cognitive and behavioral deficits that children with an FASD experience include mental health problems, disruptive school experience, alcohol and drug addiction, interaction with the judicial system, and inappropriate sexual behavior (5;6;33;36-47). The impact of FASD is wide reaching, touching the life of the individual and the lives of family members and society as a whole with major economic, social, and medical impacts in Alberta and Canada (2;48;49). The estimated additional lifetime costs associated with education, disability, assisted living, incarceration, and health care per individual with FAS or FASD vary by method of calculation and jurisdiction between $1-3.0 million Canadian (8;48;50;51). In a recent Alberta Health and Wellness report the government reported that 29% of children in government care and at least 60% of the prison population suffer from the effects of an FASD (48). This is consistent with a case-finding study in the juvenile justice system in British Columbia that found that at a minimum 23.3% of youth remanded for forensic psychiatric assessment in a one year period (n=287) had a diagnosis of an FASD (17).

Current medical guidelines in North America advise that women who are pregnant or trying to conceive abstain from alcohol and drugs as a minimal ethanol dose that can result in an FASD or deficit associated with prenatal exposure has not been identified (52-55). The effects of alcohol are variable and likely depend on quantity, frequency, and timing of exposure and maternal and fetal constitution and genetics (56-67). No safe lower level of prenatal alcohol exposure has been determined (4;23-25;68-

74). However, studies reveal that during the first trimester, sometimes before pregnancy recognition, alcohol use is reported by 12% - 60% of women, and in the month preceding delivery use of illegal drugs by up to 8.8% of women, with potentially devastating fetal impact (69;70;75). Maternal characteristics and neonatal behavior do not reliably identify infants with prenatal alcohol exposure making the early diagnosis of an FASD challenging (76-78).

The diagnosis of any given patient with an FASD is complex and often does not occur until school age, if at all, at which point benefit from intervention and support may not be realized (6;9;47). Early identification of infants affected by prenatal alcohol exposure is difficult because overt facial dysmorphic features of thin upper lip, indistinct philtrum, microcephaly, short palpebral fissures, and epicanthal folds, as well as, cognitive and behavioral deficits may not be evident until school age (5;6;9;47;79-81). Several diagnostic approaches have been developed for FAS/FASD including the 4-Digit Diagnostic Code, Institute of Medicine and the Canadian Guidelines for Diagnosis for Fetal Alcohol Spectrum Disorder (34;35). However a reliable report or record of prenatal alcohol exposure is required for all approaches and there is some variation in the ultimate diagnosis that will be given to the child depending on the method used (34;35). In addition some children may not have the full extent of the physical or developmental characteristics of FAS but may instead have deficits in the spectrum of FASD which may not be easily identifiable making early intervention challenging.

The prevalence of alcohol and drug use exceeds that identified through self-report or by targeted screening (82-85). Partly because self-report of alcohol use may be influenced by fears regarding child apprehension or social desirability self-report may

identify only 25% of those who drink in the absence of a standard approach (82;86). To aid in the identification of at risk pregnancies, alcohol screening questionnaires have been developed including the TWEAK, AUDIT and T-ACE of which the T-ACE, a four question screening tool, has been identified as a sensitive and specific tool for identifying 'at risk' drinkers in the periconceptional population (87-91).

To address the issue of under-identification of substance exposed infants, the analysis of infant biomarkers in hair, urine and meconium has recently been considered (92-99). Meconium, which is usually passed by an infant in the first 24 hours of life, is a dark black or green, viscous, odorless material that begins to accumulate in fetal intestines at approximately 20 weeks gestation and is composed of intestinal secretions, amniotic fluid, fatty material, and xenobiotics that the fetus is exposed to *in utero* (100). Thus meconium may be a good biological record of exposure for the last 20 weeks of pregnancy and may serve as a potential medium to examine for markers of prenatal drug and alcohol exposure. The putative markers for alcohol exposure in meconium are fatty acid ethyl esters (FAEEs) which are non-oxidative metabolites of alcohol that remain stable in meconium (93;95). Fatty acid ethyl esters do not cross the placenta and are therefore thought to be an indication of fetal ethanol exposure (101). In addition, only select tissues including fetal heart and brain can metabolize alcohol to FAEEs leading some to conclude that FAEEs in meconium are a sign of fetal brain exposure to alcohol (101-103). Finally, FAEEs are cytotoxic and it is hypothesized that FAEEs may be involved in damage to the fetal brain associated with alcohol exposure (103-106)

Klein *et al* reported higher concentrations of FAEEs in the meconium of a newborn whose mother reported daily binge drinking(≥5 drink per occasion) in the third

trimester (13,126 ng/g versus 410 ng/g in controls) (95). Bearer *et al* analyzed various types of FAEE in meconium in a study of non-alcoholic women and compared FAEE concentrations to self-reported alcohol use at several points prior to and during pregnancy. The specific FAEEs, ethyl linoleate and ethyl oleate were associated with a higher level of self reported alcohol use (92;93). They found that the sensitivity of FAEE analysis of meconium was 72 % and the specificity was 51 % in distinguishing those who had at least one drink per week in the third trimester from those who abstained depending on the FAEE concentration used to indicate a positive test. Alcohol consumption prior to pregnancy (at least one drink per week) was used to indicate risk of elevated FAEE resulting in a sensitivity of 68% and a specificity of 48%. In later studies the authors reported that concentrations of specific FAEEs, linoleic and oleic acid, increased in a dose-dependant manner with increases in maternal self-report of alcohol use (94). More recently Bearer *et al* reported FAEE testing sensitivity between 84-88% and specificity of 64-83.3% for drinks per drinking day and Chan *et al* reported a sensitivity of 100% and specificity of 98.4% in a group of confirmed alcoholic women as compared to abstainers for total FAEE concentration (93;107-109). However, it is unclear how timing and type of drinking affects the FAEE profile (e.g., amount and type of FAEEs) in meconium and whether or not FAEE concentration identifies children at risk for developmental delay.

Assaying for biomarkers in hair, urine or meconium of neonates may identify children at risk for deficits much earlier than previously possible, and assist in the targeting of interventions, and will provide information about maternal alcohol and drug use. Targeted urinalysis of newborns for drug metabolites is already routinely used on some postpartum units, however, there is considerable regional variation in how and

when testing is performed, how results are used, and whether consent is required (110-112). In the absence of a universal screening program it is unclear under what circumstances screening should be performed, whether informed consent from a mother is required, and whether it is ethical to obtain a neonatal sample without consent when it identifies maternal behavior (i.e., *de facto* test of mother). In addition, there is the potential for discrimination in the use of targeted alcohol and drug screening (83;110;112).

1.2 Study Rationale

Factors which can minimize secondary disabilities for a child with a prenatal alcohol exposure include early diagnosis, access to resources, involvement in special education, and a stable and nurturing care giving environment (5;6;33;47). To access resources individuals must first be identified. Currently there is a paucity of research pertaining to biological tests that reliably identify infants at risk for health and developmental problems associated with prenatal alcohol exposure. There are no studies that examine the association between concentration of a biomarker for alcohol use and early developmental outcomes and neurodevelopmental problems. There have been follow-up studies of infants whose mothers reported alcohol use in pregnancy or mothers whose medical charts indicated a history of alcoholism, however, this excludes a proportion of the population that may continue to drink during pregnancy but who are not considered excessive in their consumption, and/or in whom alcohol use is not recorded. There is conflicting evidence on the type and amount of alcohol use that results in developmental delay. Screening for biomarkers in neonate meconium in combination

with maternal self-report may provide information about maternal drug and alcohol use, identify children at risk for deficits, help to target interventions for the child and mother (e.g., maternal counseling to moderate the amount of alcohol and drugs used in subsequent pregnancies), provide insight into the mechanism of damage associated with alcohol and drug use, and improve the understanding of the relationship between FAEEs, self-reported prenatal alcohol use and developmental outcomes.

The World Health Organization (WHO) developed criteria that a screening program should ideally meet including the acceptability of the program to the target population (113). Currently, in Canada there is no clearly defined universal policy on the screening of infants for alcohol and drug exposure or for the process of consent in such a program. If jurisdictions in North America are interested in using alcohol and drug screening as a tool to target interventions and secondary disabilities associated with prenatal alcohol and drug exposure, then issues related to acceptability of the program and informed and willing consent to screening should be identified (114).

1.3 Purpose

1.3.1 The Association between Maternal Self-report and Biomarker Concentration in Meconium

The association between maternal self-reported alcohol and drug use and the concentration of FAEE and drug metabolites in meconium as well as the association between maternal and neonatal characteristics and the concentration of FAEE in meconium was examined.

1.3.2 Biomarker Concentration and Child Development

The association between FAEE concentration in meconium and child motor, mental, and social/behavioral development at 2 years of age was examined

1.3.3 Maternal Willingness to Consent to Screening of their Newborn

This study examined (1) the conditions under which postpartum women giving birth in an urban center would consent to alcohol and drug screening of their infant, (2) whether self-reported prenatal alcohol use affected willingness to consent, and (3) characteristics of women who would consent.

1.4 Research Questions

1.4.1 The Association between Maternal Self-report and Biomarker Concentration in Meconium

1.4.1.1 Primary Research Question:

- Is there an association between maternal self-report of alcohol use and concentration of fatty acid ethyl esters, a putative biological marker for prenatal alcohol exposure, in meconium?

1.4.1.2 Secondary Research Questions:

- Is there an association between T-ACE score, a clinical tool used to screen for alcohol dependence, and self-reported alcohol use during pregnancy?
- Is there an association between maternal self-report of drug use and concentration of biological marker, fatty acid ethyl esters, in meconium?

1.4.2 Biomarker Concentration and Child Development

1.4.2.1 Primary Research Question:

- Is there an association between FAEE concentration in meconium and motor and mental outcomes as determined by the Bayley Scales of Infant Development, second edition (BSID-II) at 24 months of age?

1.4.2.2 Secondary Research Questions:

- Are specific FAEEs associated with mental, motor or behavioral outcomes as determined by the BSID-II at 24 months of age?;
- Is there an association between FAEE concentration in meconium and behavioral outcomes as determined by the Child Behavior Checklist/1½-5 (CBCL/1½ -5) at 24 months of age?;
- Is there an association between FAEE concentration in meconium and temperament outcomes as determined by the Toddler Temperament Scale at 24 months of age?;
- Is there an association between FAEE concentration in meconium and adaptive behavior outcomes as determined by the Adaptive Behavior Assessment System and Temperament and Adaptive Behavior Scale at 24 months of age?;
- Is there an association between maternal self-report of alcohol use and mental, motor and behavioral outcomes as determined by the BSID-II at 24 months of age?; and
- Is T-ACE score associated with BSID-II score at 24 months of age?

1.4.3 Maternal Willingness to Consent to Screening of Their Newborn

1.4.3.1 Primary Research Questions:

- What are the conditions under which postpartum women would consent to alcohol screening of their newborn infant's meconium, hair, or urine?
- Is there a difference in willingness to consent between women who report alcohol use and those who do not?

1.4.3.2 Secondary Research Question:

- What demographic and lifestyle characteristics affect a woman's willingness to consent to alcohol and drug testing of their newborn infant?

Chapter Two: Literature Review

A search of several bibliographic search engines, including MEDLINE, EMBASE, CINAHL, and PUBMED from their inception dates, was performed in May 2002 and again in November 2006 using the OVID interface. Keywords included *meconium, ethanol, alcohol drinking, alcoholism, biological markers, fatty acid ethyl esters, substance-related disorders, cocaine, cannabis, amphetamine, pregnancy, mass screening, neonatal screening, T-ACE, self-report, self-disclosure, follow-up studies, child development, cognition, child behavior, developmental disabilities, psychomotor performance, temperament, mother-child relations, informed consent, parental consent, ethics, legal cases,* and *fetal alcohol syndrome*. Titles and abstracts of articles were reviewed for relevance. The reference lists of included full text articles and previously published reviews on the topic were examined, and relevant abstracts and articles retrieved. Recent review articles were used to identify relevant articles in the area of alcohol screening questionnaires, drug and alcohol biomarker analysis, Fetal Alcohol Spectrum Disorder, follow-up studies of drug and alcohol exposed infants, the assessment of child development, and consent in drug and alcohol testing. The purpose of the literature review was to: 1) review the impact of alcohol and drug use in pregnancy on the fetus, infant, child and adult; 2) identify and review tests and screens for alcohol and drug use in pregnancy; 3) examine the evidence for the association between indicators of alcohol use during pregnancy and child development; 4) identify and review tests for assessing child development at a young age; and 5) identify studies that examined issues related to perinatal testing or screening and the consent process.

2.1 Fetal Alcohol Spectrum Disorders

2.1.1 Pathophysiology of Prenatal Alcohol Exposure

In 1968 Lemoine *et al* first described in scientific detail a group of children in France who presented with several characteristic features including craniofacial abnormalities, growth restriction, and neurocognitive deficits born to mothers with histories of alcohol abuse (115). The term Fetal Alcohol Syndrome (FAS) was first coined over 30 years ago by Jones *et al* to describe a similar group of children in Seattle (30). More recently, the term Fetal Alcohol Spectrum Disorders (FASD), a description rather than a diagnosis, was proposed by Streissguth *et al* to describe a range of deficits that can accompany prenatal alcohol exposure (6). Alcohol, the most commonly used teratogen worldwide, contributes to spontaneous abortion, birth defects, growth restriction and neurological deficits; however the exact mechanisms by which alcohol and its metabolites, acetaldehyde and fatty acid ethyl esters (FAEE), damage the developing fetus is unknown (22;31;76;116;117). Ethanol and its metabolites are known to interfere with metabolism of nutrients as well as with their transfer across the placenta resulting in decreased fetal growth (63;101;118;119). Teratogens disrupt normal development in offspring through exposure during pregnancy and the effect depends on the genetic makeup of the organism, timing of exposure, access to the fetus, and level of exposure (120). In the case of prenatal alcohol exposure, the specific body system affected and the long term outcomes seem to depend on when the exposure occurs. The effect of a teratogen persists into adulthood and is irreversible.

2.1.2 Growth Deficits, Birth Defects and Morphologic Abnormalities Associated with Prenatal Alcohol Exposure

Clinical features of FAS include growth restriction (pre- and postnatal), developmental delay, phenotypic facial features (e.g., ear, eye, and lip abnormalities), central nervous system deficits, and congenital anomalies, in the setting of a history of prenatal alcohol exposure (12;23;25;29;31). The facial abnormalities result from insult to the fetus when the midline of the face is formed at 3 weeks gestation (120;121). This is also a time of particular central nervous system (CNS) sensitivity to exposure. For this reason morphologic abnormalities and CNS dysfunction are strongly associated which led to diagnostic criteria for FAS including facial features of a thin upper lip, smooth or flattened philtrum, and short palpebral fissures in combination with CNS deficits (34;35;122-124). A case finding study for FAS in the foster care population that utilized analysis of facial features alone had a sensitivity of 100% and a specificity of 99.8% for FAS (124). Essentially, facial features consistent with FAS are an outward sign of damage to the fetus at a time of CNS particular sensitivity to ethanol and suggest that a patient with these features needs to be evaluated for cognitive delay.

Several animal studies and human follow-up studies have examined the association between prenatal alcohol and drug exposure and physical and neurological development. In a model of FAS in which mice were fed alcohol to the equivalent of 4 or 5 drinks, the definition of a binge episode, infant mice had changes to the face, eyes, inner ear and brain, that parallel changes that have been seen in human infants exposed to prenatal binge episodes (125-127). In general, children with FAS are small for their age and growth restriction and post-natal growth deficit, often symmetrical, with birth weight

or length at or below the 10th percentile and height or weight at or below the 10th percentile are one of the diagnostic criteria for FAS (34;35;122-124). A growth deficit may persist into late adolescence but is not as evident in adulthood (128). In the Maternal Health Practices and Child Development Project, a longitudinal study of the long-term effects of prenatal alcohol exposure where drinkers were defined as anyone having 3 or more drinks per week in the first trimester, identified a dose-dependant relationship between maternal alcohol consumption and growth deficits in height, weight and head circumference (129;130). This effect has been seen across different populations including marginalized populations and advantaged populations (1;65;129-138). Another study found that the association between fetal alcohol exposure and growth deficits only holds for women over 30 years of age (138;139). The authors concluded that postnatal and maternal characteristics contribute to observed effect (138;139). The association between prenatal exposure and growth deficit is seen across social strata indicating that maternal SES does not protect against or eliminate the deleterious effects of alcohol exposure. In addition, maternal age may be an important modifier of that association.

2.1.3 Central Nervous System Deficits/Cognitive Development Associated with Prenatal Alcohol Exposure

Neurobehavioral deficits associated with alcohol exposure may result from drinking at any time during pregnancy and following pregnancy if a breastfeeding mother consumes alcohol and breastfeeds her infant while her blood alcohol level (BAL) is still elevated (140-143). Prenatal and perinatal alcohol exposure can result in a lasting change of structure and function of the central nervous system including exposures that affect

cytogenesis and cell migration of the neural crest in the first 20 weeks gestation and those that affect brain growth, differentiation and degree of neuronal apoptosis in the last 20 weeks of gestation (120;126). A single exposure to alcohol at binge-drinking levels in infant mice results in apoptosis and neurodegeneration in many parts of the brain with damage to areas of learning and memory that are similar to those seen in the alcohol-exposed human brain (126;144;145). Brain damage resulting in problems with learning and behavior similar to those seen in children with FAS can also be seen in rat pups when they have been prenatally exposed to a single binge-drinking episode (146-148). In addition, at alcohol exposure levels equivalent to only one drink per day no physical defects or decrease in birth weight were seen but problems with learning and behavior were observed (146). Therefore there is evidence of CNS damage presenting as delays in learning and behavior in animal models for “low-dose” and binge alcohol exposure (146).

No single type of CNS damage has been identified that characterizes FASD. Fetal alcohol spectrum disorder-related problems are associated with underlying structural or functional changes in the brain, reduction in overall brain size, damage to the basal ganglia, reduced size of the cerebellum, and reduction or absence of the corpus callosum. These changes result in problems with balance, gait, coordination, cognition, behavior, intelligence, memory, language, gross and fine motor control, executive functioning, social skills and communication between the right and left halves of the brain (5;39;149-163). Exposed neonates who do not have an FASD may have disturbed sleep patterns and an impaired ability to adapt and respond to external stimuli as measured by the Brazelton Neonatal Behavioral Assessment Scale (164). Gusella and Fried, in a study of 84 thirteen month olds of the Ottawa Prenatal Prospective Study, found that ‘low’ levels (average

across pregnancy of less than one drink per day) of alcohol exposure were significantly associated with poorer mental development, as determined by BSID (165). At 2 years, the association was still significant, but by 36 and 48 months low levels of alcohol exposure were no longer associated with poorer mental development (131;133;134). However, at 48 months motor deficits were significantly associated with low levels of exposure (133). In preschool, an alcohol exposed child may present with hyperactivity, impulsivity, poor cooperation, poor eye-hand coordination, poor balance, poor tandem gait, central auditory dysfunction, mental retardation, and delayed or preservative language (9;80;131;165).

Intelligent quotient is often used as a general assessment of child development in follow-up studies of children prenatally exposed to drugs and alcohol (160;166-168). In addition, general mental ability measures like the Mental Development Index (MDI) of the Bayley Scales of Infant Development (BSID-II) are used as a global assessment tool. Aronson *et al* followed-up children of women diagnosed with alcohol dependence (typified by compulsive drinking behavior, tolerance to alcohol, withdrawal, and dysfunction in interpersonal or professional life as a consequence of alcohol use) and found that they had a mean IQ of 95 while the children of abstaining mothers had a mean IQ of 112 (169). The children studied by Aronson *et al* were not diagnosed with FAS and mothers did not necessarily drink heavily during pregnancy. In addition, children of mothers with a diagnosis of alcohol dependence had delayed visual-perceptive ability, hyperactivity, and distractibility (169).

There appears to be a continuum of IQ deficit for children with prenatal alcohol exposure with children with a diagnosis of FAS typically lower than other children. Streissguth *et al* found in a sample of 61 children (ages 5 to 14) with a diagnosis of FAS

that the mean IQ was 68 with a range from 29 to 120 while children diagnosed with FAE (partial FAS) or ARND had a mean IQ of 90 (160). Children not diagnosed with FAS or FAE (partial FAS) who were exposed to 1 to 2 drinks per day had an IQ that was 7 points lower than a non-exposed comparison group at age 7 (160). It also appears that there is a range of deficits in children in the literature associated with self-reported prenatal alcohol use of 1-2 drinks per day from 7 to 24 IQ or BSID MDI points (59;133;134;155;170-172). A recent meta-analysis of studies examining self-reported prenatal alcohol use and MDI found association at 12 months but not at 18 or 24 months(173). The association in this age range may have been obscured by challenges in assigning children to 'exposed' and 'unexposed' groups based on maternal self-report, an inaccurate method of ascertaining exposure.

2.1.4 Behavioral Development of Children with Prenatal Alcohol Exposure

Some researchers in the area of FASD feel that adaptive behavior and social judgement are the greatest impairments that affected children and their caregivers have to deal with (5;159;160;166;171;174;175). Teenagers with FAS have behavioral problems, decreased social competence, and poor school performance and display social skills and interpersonal relationship skills equivalent to a normal 6 year old, independent of IQ (5;162;175). Several large cohort studies have found that prenatal alcohol exposure is associated with the following in children: poor socialization, conduct problems, attention deficits, hyperactivity, anxiety, and depression (5;130;172;176;177). In a large study (n=501) of 6 to 7 year old African-American children examining the effects of 'low' level alcohol exposure on child behavior outcomes as assessed by the Child Behavior Checklist

(CBCL), Sood *et al* found that there were deficits in behavior associated with prenatal alcohol exposure but not IQ (172). Alcohol exposure was adversely related to behavior at levels as low as 1 drink per week averaged across pregnancy when controlling for the confounding variables of maternal age, education, cigarette use, cocaine use, gestational age, maternal psychopathology, ongoing drug and alcohol use, family structure, socioeconomic status (SES), child's whole blood lead level and exposure to violence (172). Specifically, children with low levels of prenatal alcohol exposure were more likely to have an increase in externalizing and aggressive behaviors while an increase in delinquent behavior was with children exposed prenatally to an average of 1 drink per day (172). In summary, a single neuropsychosocial profile cannot characterize all children prenatally exposed to alcohol and behavioral deficits cannot be fully explained by an IQ deficit. However, at 'low' levels of exposure deficits in behavior have been demonstrated in several studies.

2.1.5 Risk Factors for Deficits Associated with Prenatal Alcohol Exposure

The role that maternal lifestyle, genetics, and fetal characteristics play in fetal vulnerability to FAS/FASD remains to be determined. Fetal alcohol syndrome has been diagnosed in the children of women from all racial, educational and SES strata of North American society (36). However, the following maternal and fetal characteristics have been examined in the literature and are thought to potentially influence the impact of prenatal alcohol exposure on outcomes: socioeconomic status, education, marital status, maternal age, parity, diet, patterns of alcohol use, tobacco use, poly-drug use, the timing, pattern, and dose of alcohol exposure and prenatal diet (36;72-74;116;172;178-186).

Although FAS is often considered to be a health problem for Aboriginal populations there is no evidence that there is an ethnic or genetic basis for this (13;187). It is unclear what proportion of exposed fetuses are affected by exposure to alcohol, but one study found that 40% of alcoholic women, women who drank at a binge level daily and had significant dysfunction in their lives because of their alcohol use, gave birth to infants with FAS/FASD indicating that exposure alone will not result in damage consistent with FAS in all cases (77;116). It is estimated that a mother with one child with FAS has an 80% percent change of having subsequent children with FAS (77). This may be in part due to the challenge in modifying behavior related to addictions.

A recent study generated evidence related to a minimum dose that may result in FAS that is much lower than conventionally thought. In a case-finding study in Italian urban schools May *et al* that reported a prevalence of FAS of 3.7 to 7.4 per 1,000 children and a prevalence of FASD of 20.3 to 40.5 per 1,000 children. Mothers with a child with a diagnosis of FAS reported consuming a mean of 16 drinks/week at time of assessment while mothers with a child who had no alcohol related diagnosis reported 1.5 drinks per week (18). The authors argue that contrary to popular opinion a drinking pattern of daily drinking with meals at a level of 2 drinks per day can result in deficits, including even a diagnosis of FAS (18).The report of 16 drinks/week may be more accurate than reported alcohol use obtained from studies in North America as there is less stigma associated with alcohol use during pregnancy in Europe. A diagnosis of FAS therefore can be associated with a much lower intake of alcohol during pregnancy than previously thought. The findings of this study call into question the policies on prenatal alcohol use of several countries including Australia and the United Kingdom which only

recommends that pregnant women limit their alcohol intake to 1-2 units once or twice per week and that women should avoid getting drunk during pregnancy (188). This recommendation is only ¼ the mean weekly dose that was found to be associated with a diagnosis of FAS in the study by May *et al* suggesting that absolute abstinence may be a more appropriate message (18).

The association between frequent binge drinking and consistent 'high' levels of alcohol consumption during pregnancy with mental, motor, and behavioral delays is well established (59;189). However, it is unclear if and how much of a deficit occurs with doses of 1 drink per day or occasional drinking. The impact of low dose, long term exposure may be clinically significant and in human studies and animal models very low doses of alcohol (e.g., less than one drink per day averaged across pregnancy) have been associated with attention, memory, behavior, and information-processing deficits as well as physical deficits from birth to adulthood (1;65;76;131-136;164;165;190).

2.1.6 The Impact of Polydrug Use on Infants

Combining alcohol use with the use of other substances like cannabis, opiates, amphetamines, phencyclidine (PCP) and cocaine (e.g., crack) may further compromise the developing fetus (19). Although marijuana has not been correlated with teratogenic effects; its use has been associated with the use of other drugs that have been so women who report marijuana use should be interviewed carefully about drug and alcohol use. Cocaine and amphetamines are stimulants of the central nervous system and can have a dramatic negative effect on cardiovascular tone and are associated with abruption, preterm labor, precipitous labor, meconium aspiration syndrome, fetal demise and

stillbirth (19-21;168;191;192). A recent study found that children exposed to cocaine *in utero* had significant cognitive deficits and an increased rate of developmental delay as compared to unexposed children (192). Heroin use has been associated with intrauterine growth restriction, low birth weight, microcephaly, prematurity and miscarriage (193). Any study that examines prenatal alcohol exposure and developmental outcomes should control for the potential impact of poly-drug use.

2.1.7 Confounding or Contributing Variables for Poor Child Development Associated with Prenatal Alcohol Exposure

Child development is dependent on many factors. In studies that examine the association between a prenatal exposure and child development it is crucial that all potentially relevant confounders or effect modifiers be accounted for. Variables that are frequently controlled for or that are predictive of child development include the following:

- SES (129;130;133;134;168;172;194);
- Maternal IQ and education (192;194;195);
- Alcohol use while breastfeeding and after delivery (142;143;172);
- Maternal drug use (120;168);
- Parent-child interactions and nurturance (196-198);
- Maternal smoking (1;133;134;199-201);
- Breast feeding duration (202);
- Caffeine use (1;78;142;203);
- Nutrition (201);

- Low birth weight (136;204-206);
- Prematurity (191;207-209);
- Temperament (210);
- Gender (1;133;134;164;211);
- Birth order (1;212); and
- Severe child illness/congenital malformation (Often an exclusion criteria) (172).

2.1.8 Early Diagnosis and Early Intervention

There is some evidence that early diagnosis and access to early interventions reduces the risk of some prenatal alcohol exposure-related disabilities (5;33;47). A retrospective cohort study by Streissguth *et al* found in a large sample (n=415) of children and adults with an FASD that those who were diagnosed before the age of six had a lower rate of secondary disabilities. Those diagnosed early and raised in a stable environment were 2 to 4 times less likely to have adverse life events (47). Adverse life events for those who were not diagnosed with an FASD early included trouble with law (60%), institutionalization (50%), inappropriate sexual behavior on repeated occasions (49%), alcohol and drug problems (35%), and disrupted school experience (61%) (47). There is consensus in the literature and among experts in the area of FASD that early diagnosis is a protective factor which can minimize secondary disabilities as it may lead to early intervention and access to specialized services (9;29;47). To access such resources individuals must first be identified.

However, early identification of the physical stigmata of FASD is challenging because of the difficulty inherent in assessing dysmorphology in infants. In addition,

there is considerable challenge in determining if a deficit is due to alcohol exposure versus a multitude of developmental and environmental disorders. It is apparent from the review of the literature that there is a need for an objective test that can identify infants at risk for disabilities associated with prenatal alcohol and drug exposure including physical abnormalities, developmental delays, mental health problems, and disruptive school experience.

2.2 Epidemiology of Alcohol and Substance Use in Pregnancy

The current recommendations from health and medical organizations in North America are that women abstain from alcohol if they are pregnant or are attempting to conceive because no safe lower level of alcohol consumption during pregnancy has been determined (4;24;25;52;53;188;213;214). Regrettably, a proportion of women, estimated at between 4 and 27%, continue to drink alcohol and use drugs during pregnancy and the effects on the fetus can be devastating (4;69;72;73;179;213;215-218). In Canada, rates of alcohol consumption during pregnancy have been estimated using the 1996-1997 National Longitudinal Survey of Children and Youth (NLSCY). In the prairie provinces, approximately 16.1% of women with children under the age of 3 years reported drinking during pregnancy, while 16.6% of women in Canada reported some drinking during their pregnancy (69;70;216). In the same survey, 22.6% of women over 35 years of age reported drinking during pregnancy while only 11.7% of those under the age of 25 reported drinking during pregnancy (69;70;216). In the National Institute on Drug Abuse (NIDA) 1988 survey 8.8% of women of childbearing age reported using street drugs in the month preceding delivery and 30% of women 18 to 34 reported use of a street drug in the preceding year (219). With no confirmation of drug use via laboratory testing, Teagle and Brindis describe an incidence of drug use via self-report in adolescent pregnant mothers as high as 79% (84). In a sample of 876 American women 15% of the mothers at a teaching institution and 3% of the mothers at a private institution reported using cocaine during pregnancy (220). In Canada, cannabis is the most widely used street drug with highest rate of use reported among women 15-24 years of age with 25% at age 15 to 19% at age 24 (221). This survey did not discuss many potentially important factors of

prenatal alcohol exposure, including timing, frequency or regularity of consumption, and binge patterns.

There are reports that suggest that women who engage in binge and risk drinking during or prior to pregnancy recognition are not planning a pregnancy, are not using assisted reproductive technology, have a higher income are more likely to smoke cigarettes, and use various illicit substances (e.g. stimulants, cannabis, opiates, hallucinogens, and inhalant) and are young and single (18;72-74;178-181;222-229). Additional risk factors for drug and alcohol use during pregnancy include history of sexual, physical or emotional abuse, depression, low self-esteem, low and high maternal education, high maternal age, being single, maternal ethnicity, low and high socio-economic status and limited prenatal care (18;72-74;178-181;222-227;229). However, no single profile identifies all women at risk.

A recent report from Tough *et al* describes a population-based sample of Canadian women of childbearing age in which 80% consumed alcohol and 62% continued to drink until pregnancy recognition (229). Overall, 50% of all women continued to drink until they recognized that they were pregnant (229). Approximately 20% of these women continued to drink post-pregnancy recognition and 1/3rd of the women had a binge drinking episode at a time when they were at risk for pregnancy (229). Women over 30 years of age were more likely to continue drinking small amounts of alcohol following pregnancy recognition (229). It evident from the literature that some Canadian women maintain an alcohol use pattern until pregnancy recognition that potentially places their fetuses at risk for deficit associated with prenatal alcohol exposure.

2.2.1 Interview Methods of Identifying Alcohol and Drug Use

2.2.1.1 Self Report of Alcohol and Drug Use

It is believed that maternal self-report of alcohol and drug consumption is unreliable and underestimates the true prevalence in the maternal population (82;86;230). The reporting of alcohol consumption and drug use may underestimate the true prevalence of prenatal alcohol use by as much as a factor of five, due to difficulty in recall, shame, fears regarding child apprehension, social desirability, lack of understanding of the effects of use on the unborn growing fetus, denial of the problem by the women and those close to them, lack of accessible treatment, and inconsistent screening for alcohol and drug use during pregnancy (82;86;100). Self-report depends on a mother responding truthfully and on a clinician asking the question (82;86). An assessment of alcohol and drug consumption can depend on the attention that the clinician devotes to the interview (82;86). Little *et al* examined the agreement between self-reported use of alcohol, tobacco, marijuana and psychoactive drugs with blood and urine tests in 108 postpartum women (78). There was high correlation between self-reported regular use and positive tests but much lower correlation when use was reported as infrequent (78). An informal interview of a mother inquiring about alcohol and drug exposure results in under-reporting, whereas a more formal and organized interview increases reporting five-fold (82;86). A more standardized means of ascertaining maternal risk for alcohol and substance abuse is required if pregnancies at risk are to be identified.

In a prospective study of 3010 infants from an inner city population, 31% of meconium samples were positive for cocaine, 21% were positive for opiates and 12%

were positive for canniboids (99). A significant number of infants who did not present with any symptoms of exposure had in fact been exposed as determined by the presence of drug metabolites and mothers denied use of drugs. Only 11% of mothers had reported drug use suggesting missed opportunity for routine improved early identification of women at risk using standardized methods (99).

2.2.2 Standardized Tools to Screen for Alcohol Use

To aid in the identification of at risk pregnancies and to overcome the biases and inaccuracy inherent in self-report, alcohol screening questionnaires have been developed including the TWEAK, AUDIT, SMAST, CAGE and T-ACE. These tools can be administered and scored in less than 5 minutes and each scale has been validated in different populations and has varies in its sensitivity and specificity (87-91). When comparing AUDIT, SMAST and T-ACE, the latter was the most sensitive for previous diagnosis of alcohol dependence or abuse, risk drinking, and current alcohol consumption (90;91). The TWEAK and T-ACE have been evaluated among pregnant women and both tools have been found to be highly sensitive and are considered more sensitive than clinician interview for detecting periconceptional alcohol use (90;91).

The T-ACE, which has been incorporated into prenatal records in Alberta, is a four question screening tool to identify at risk drinkers in the periconceptional population (89). The T-ACE includes the following items:

- T-tolerance – How many drinks does it take to make you to feel high? A response of greater than 2 drinks = 2 points with 2 drinks or less=0;

- A-Annoyed – Have people annoyed you by criticizing your drinking? Yes=1 point;
- C-Cut down – Have you felt that you ought to Cut down on your drinking? Yes=1 point; and
- E-Eye opener – Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? Yes=1 point (17).

A positive T-ACE score (defined as a score 2 or greater) is believed to correctly identify over 70% of mothers who were heavy drinkers during pregnancy (88;89). Among those who score 2 or greater the sensitivity (proportion of women who drink during pregnancy who have a positive screen) is 70-88% and the specificity (proportion of women who do not drink during pregnancy who have a negative test) is 79-85% (88;89).

2.2.3 Biomarkers for Alcohol and Drug Use

Several biomarkers of alcohol and drug use have been examined by researchers. Biomarkers of maternal drinking can be broken down into three categories: biomarkers of exposure, biomarkers of susceptibility, and biomarkers of effect (215). Biomarkers of exposure detect exposure rather than the effect of an exposure. Fatty acid ethyl esters are an example of putative biomarkers of exposure for maternal alcohol use. Biomarkers of susceptibility mark an increased susceptibility in the pathway between exposure and disease. Biomarkers of effect detect the effect of an exposure. In the case of alcohol exposure, FAS is a marker of late effect. Examples of biomarkers of early biological effect are cellular changes and organ damage associated with alcohol use (231).

Infant urine and meconium testing can be used to detect maternal alcohol and substance abuse; however urine testing affords less accuracy in the detection of drugs and alcohol as compared to meconium testing. Meconium may only be reflective of alcohol and drug use in the last half of pregnancy and therefore does capture early substance use or a binge pattern that stops following pregnancy recognition. Thus meconium maybe a good biological record of exposure for the last 20 to 23 weeks of pregnancy and may serve as a potential long-term marker of prenatal alcohol and drug exposure but would not be reflective of alcohol and drug use at time of conception and at 3 weeks when CNS sensitivity to insult is high. Infant urine toxicology screening can assess prenatal exposure in the 3-7 days prior to delivery. More recently, assay methods for biological markers of drug use in meconium have been developed (92;94-98;100;107-109;215;232-236). Bibb *et al* recommend that urine testing be abandoned in favour of meconium testing based on findings from 580 mother/infant pairs where the correlation between meconium drug screen and self-report was much higher than for urine drug screen and self report (237). In their large scale study of 3010 inner city women, Ostrea *et al* demonstrated detection of drug use in 52% of urine samples as compared to 88% of meconium samples (99). In a related study Ostrea *et al* compared the sensitivity and specificity of maternal interview data, maternal hair analysis and meconium analysis in the detection of perinatal drug exposure; specifically, cocaine, opiate and cannabinoids, in 58 women (238). Maternal interviews had the lowest sensitivity for cocaine (65%) and opiate (67%) detection, but the highest sensitivity in the detection of cannabinoids (58%) (238). Meconium had a 87% sensitivity for cocaine and 77% sensitivity for opiates, with

no false positives; whereas hair analyses had a 13% false positive rate for cocaine and a 20% false-positive rate for opiates(238).

Fatty acid ethyl esters are produced in a secondary metabolic pathway by an enzymatic process involving esterification of alcohol with free fatty acids and can be found in meconium (85;92;94;97;98;100;102;195;235;239-241). Alcohol crosses the placenta and rapidly reaches the fetus while fatty acid ethyl esters do not cross the placenta and are therefore thought to be an indication of fetal ethanol exposure (101). Several studies have demonstrated that a fetus has the same blood alcohol level (BAL) as the mother and given that the fetal liver and alcohol dehydrogenase (ADH) function at approximately 5% of the adult liver, exposure to alcohol may be prolonged (101;242). In addition, only select tissues including fetal heart and brain can metabolize alcohol to FAEEs leading some to conclude that FAEEs in meconium is a sign of fetal brain exposure to alcohol (101-103;243). Finally, FAEEs are cytotoxic and it is hypothesized that FAEE may be involved in damage to the fetal brain associated with alcohol exposure (101-103;106). Fatty acid ethyl esters detected in neonatal tissues and metabolic products are likely produced by the fetus from ethanol that has been transferred to and metabolised by the fetus (101). Fatty acid ethyl esters in serum have recently been used as biomarkers of acute and chronic alcohol consumption in adults and have been reported to accumulate in the blood of adult drinkers (244). However, it is unclear how timing, dose and type of drinking affect the FAEE profile in meconium other than that exposure in the first 17 to 20 week of pregnancy will not be captured. In addition, the role of maternal life style, genetic characteristics, diet, and patterns of alcohol use on concentration and type of FAEE in meconium remains to be determined. It is important to note that FAEEs have

also been identified in meconium from newborns of abstaining mothers perhaps due to endogenous alcohol production. Studies that have examined FAEEs in meconium are summarized in Table 2.1.

Table 2.1. Overview of human FAEEs in meconium studies conducted to date

Reference	Comparison	Sample	Analysis	Result
Mac *et al* (245)	Exposed (maternal report) vs. control	Control (n=10) Exposed (n=15)	GC:MS*	Exposed children had higher concentration of FAEE
Bearer *et al* (246)	Exposed (maternal report) vs. control	Control (n=40) Exposed (n=21)	GC:FID	Proportion of FAEE≥2 nmol/g 43% in exposed versus 40% in control
Bearer *et al* (93)	High risk clinic based sample	248 subjects with varying exposure	GC:FID **	Sensitivity 72% & specificity 51% for 1 or more drink/week in 3rd trimester
Klein *et al* (95)	Case study of high risk women	Controls (n=3) Exposed (n=1)	GC:FID	FAEE 13,126ng/g in exposed versus 410 ng/g in control
Moore *et al* (98)	Anonymous sample	30 samples	GC:MS	FAEE≥50 ng/g labelled positive
Moore *et al* (97)	Anonymous sample	Hawaii (n=436) Utah (n=289)	GC:MS	16.7% of samples positive with cut off of 500 ng/g
Derauf *et al* (247)	Prevalence study	436 mother-infant dyads	GC:MS	Kappa= -0.02, no agreement
Chan *et al* (235)	Exposed (maternal report) vs. control	Control (n=207) Exposed (n=6)		Baseline FAEE in abstainers of 1.37 to 2.08 nmol/g. Exposed had mean of 11.1 nmol/g. Using a cut off of 2 nmol/g sensitivity 100% and specificity 98.4%.
Chan *et al* (108)	Anonymous sample	Clinic based sample	GC:FID	14% of samples positive above cut off of 2 nmol/g
Bearer *et al* (94)	High risk sample – South Africa	Controls (n=6) Exposed (n=21)	GC:MS	Sensitivity 84.2%, specificity 83.3% with ethyl oleate above the LOD as marker
Bearer *et al* (107)	High risk clinic based sample compared to population of abstainers	Jordan (n=30) Cleveland (n=248)	GC:FID	Sensitivity 88%, specificity 64%, PPV 9%, NPV 99% for ethyl linoleate ≥32 ng/g
Ostrea *et al* (105)	Exposed (maternal report) vs. control	Control (n=31) Exposed (n=93)	GC:MS	Ethyl linoleate ≥LOD sensitivity 26.9%, specificity 96.8% and PPV 96.2%.
Noland *et al* (248)	4 year follow up study	Exposed by maternal report and FAEE	GC:MS	Alcohol exposure by maternal report and FAEE not associated with selective attention
Noland *et al* (205)	Follow 9.5-12.5 months, polydrug exposure	Exposed by maternal report and meconium biomarkers	GC:MS	Alcohol exposed group of 4 year olds had worse tapping inhibition (executive functioning)

*GC:MS - Gas chromatography: Mass spectroscopy. **FID – Flame ionization detection.

Klein *et al* reported higher concentrations of FAEE (13,126 ng/g versus 410 ng/g in controls) in the meconium of a newborn whose mother reported significant drinking in the third trimester (95). The group also tested the meconium of three neonates who were not exposed to maternal drinking. Palmitic, linoleic, and stearic ethyl esters were found in the alcohol exposed meconium and were absent from the non-exposed samples (95). The researchers then spiked samples of meconium with ethyl alcohol to determine if FAEEs are produced in meconium on exposure to alcohol. The presence of ethyl linoleate was measured making this group the first to report the production and isolation of FAEEs from alcohol in meconium (95).

Bearer *et al* analyzed levels of various types of FAEE in meconium in a study of non-alcoholic women who self-reported varying amounts of alcohol use during pregnancy. The specific FAEEs, ethyl linoleate and ethyl oleate were associated with a higher level of alcohol use (92;93). They found that the sensitivity of FAEE analysis of meconium was 72 % and the specificity was 51 % in distinguishing those who had at least one drink per week in the third trimester from those who abstained. Alcohol consumption prior to pregnancy (at least one drink per week) was used to indicate risk of elevated FAEE concentration resulting in a sensitivity of 68% and a specificity of 48%. In later studies the authors reported that the concentrations of specific FAEEs, linoleic and oleic acid, increased in a dose-dependant manner with increases in maternal self-report of alcohol use (94). Cocaine, marijuana, and tobacco use was similar for those with elevated FAEE concentrations and those with lower concentrations of FAEE (92;93).

More recently Bearer *et al* validated their method with 23 South African women who prospectively reported alcohol use during pregnancy (94). They found that levels of

oleate were correlated with alcohol use in the 2nd and 3rd trimesters (r=0.55 and 0.40, respectively). They determined that ethyl oleate has a sensitivity of 84% and specificity of 83% and sensitivity between 84-88% and specificity of 64-83.3% for drinks per drinking day with linoleic acid (92). Chan *et al* reported sensitivity of 100% and specificity of 98.4% in a group of six confirmed alcoholic women as compared to abstainers with total FAEE concentration (93;107-109). Several studies have demonstrated that FAEE concentration can identify women who report alcohol use during pregnancy. However, there is variation between populations in terms of predominant FAEE species and whether or not specific FAEEs are indicative of alcohol exposure versus overall FAEE concentration.

2.2.4 Difficulties Inherent in Studies Involving Periconceptional Alcohol and Drug Use

The level of scientific evidence for tools to detect drug and alcohol use could best be classified as ‘some’ or ‘moderate’. The vast majority of studies are quasi-experimental with non-random control groups or case studies with no comparison group. Studies to date have varied widely in populations screened, sample size and methodology of screening. In addition, it is difficult to comment on the validity and reliability of self-report, T-ACE questionnaire, and meconium analysis as there is currently no “gold-standard” for prenatal alcohol and drug use. Self-report does not appear to be a valid or reliable method of determining maternal alcohol and drug consumption. A delimitation of using FAEE in meconium as a marker of alcohol use during pregnancy is that alcohol use prior to approximately 20 weeks gestation will not be captured. However, a self-report of

alcohol use and a positive T-ACE score may identify mothers who use drugs and alcohol early in pregnancy that meconium analysis cannot identify.

Another issue in studies related to prenatal alcohol exposure is in identifying and trying to quantify or assign a dose. Many studies average alcohol consumption across pregnancy which obscures the difference between a binge pattern and a daily intake of alcohol. For example, an average dose of 1drink per day obscures if this is based on 1 occasion per week in which 7 drinks are consumed or a daily pattern of 1 drink per day. This is an important distinction as there is some evidence that a binge exposure may place a fetus at greater risk of deficit. In addition, some studies assign exposure descriptors of ‘low’, ‘moderate’ and ‘high’ which is meaningless given that there is no evidence base for a threshold for deleterious impact on the developing fetus.

2.3 Maternal Willingness to Consent to Alcohol and Drug Testing of their Infants

Currently in Canada there is no clearly defined policy on the screening of infants for alcohol and drug exposure or for the process of consent in such a program. In addition, there is evidence that suggests the potential for discrimination against minorities and marginalized members of society in the use of alcohol and drug screening. One study of all pregnant women receiving prenatal care found that of 715 women screened by urinalysis, 14.8% tested positive for an illegal substance (83). There was no significant difference between public and private patients nor between white and black women. In general, white and black women used different drugs; 15.4% of white women and 14.1% of black women tested positive for an illegal drug. However, black women were 10 times more likely to be reported to State child welfare authorities and have their children apprehended than white women (83). The criminalization of prenatal alcohol and drug use targets the impoverished and medically and socially underserved groups (83;249).

In the absence of a universal screening program for prenatal alcohol and drug exposure a clinician must decide who is to be tested. What is involved in a clinician's decision to test in the absence of criteria for testing? It is challenging for clinicians to identify infants at risk by maternal characteristics and neonatal behavior alone in the first 24 hours (112;250;251). As the majority of mothers and infants are discharged within the first 24-48 hours after birth a neonate may not show signs of withdrawal (250;251). In addition, by the time an infant shows signs of withdrawal urinalysis will not identify drug metabolites given the rapid clearing from the infant's system. The clinician is left with several choices: Treat symptoms of withdrawal in neonates and do not test; Test all

infants and monitor infants with positive test; Test no one; or Take samples from everyone and store for analysis as warranted or symptoms indicate.

2.3.1 Maternal/Patient Rights

There are several Canadian legal and ethical precedents that should be considered in examining issues related to alcohol and drug screening of women and fetuses and the requirement for informed consent. These are discussed in detail by Flagler *et al* who concludes that in medical practice, informed consent from a competent patient prior to treatment or testing is a legal necessity (252;253). Informed consent cannot be waived by a clinician if it is difficult to obtain and clinicians are at risk for civil and criminal liability if informed consent is not obtained (252;253). Under the Canadian Charter of Rights and Freedoms women have rights to life, liberty and security of the person (254). Testing without informed consent is a violation of a woman's rights (253). The Supreme Court of Canada has ruled "the onus for proving the need for medical testing lies on those seeking to perform that testing" (252;253). The position of the Canadian Human Rights Commission is that random alcohol and drug testing is discriminatory with the exception of employees in safety-sensitive positions (e.g., airline pilot) (254). Pregnancy is not considered a safety-sensitive position. In addition, while drug use is illegal, alcohol use during pregnancy is not illegal.

Women are viewed by society to have responsibilities during pregnancy. Women are morally obligated to act in the best interest of their fetus; however, this cannot be enforced legally (252). In Canada a woman cannot be held responsible for damage done to a fetus as a fetus does not have rights until it is born alive and therefore legislation

related to child protection does not apply to the fetus (252). Often the term maternal-fetal conflict is used in describing a mother that is acting in a way that may harm her fetus. Flagler *et al* conclude that this term is inappropriate, as the real conflict exists between the pregnant woman and those who believe that her behavior is not in the best interest of the fetus (252). Clinicians, health care providers, lawmakers, and policy makers must acknowledge that alcohol and drug addiction is a disease influenced by contributing factors of poverty and minority status.

The Canadian Medical Association (CMA) and the Royal College of Physicians and Surgeons of Canada have position statements that are pertinent to this discussion. A clinician "must respect the right of a competent patient to accept or reject any medical care recommended" and is to provide counseling and persuasion when they feel that a woman is behaving in a way that is not in the best interest of the fetus but coercion is not to be used (252;255). A recent survey of 847 obstetricians, pediatricians, and family practice clinicians in the United States found that 61% to 75% agreed with mandatory screening for alcohol abuse; 43% to 55% agreed with mandatory screening for illicit drugs; and 52% favoured legislation that would make alcohol and drug use in pregnancy "child abuse" and grounds for removal to protective custody (256). It should be noted that this survey was completed prior to a US Supreme Court ruling that would prohibit mandatory alcohol and drug testing (110;257). The findings of this survey may indicate a conflict of clinician's attitudes with the ethical principles of beneficence, autonomy, and justice that should be considered in counseling or treating a pregnant woman who is using drugs or alcohol. Health care workers are obliged to promote the health of a pregnant woman and fetus and minimize harm to both. At the same time, the health care worker

must respect the patient's autonomy. Pregnant women have a right to be treated fairly and equally without their liberty being infringed. In addition, a just society does not create an environment that limits a person's choices (e.g., minimal resources to enhance health of women and fetuses) and then punish them for making a poor choice (249).

2.3.2 Alcohol and Drug Testing in Other Regions

Regional and federal authorities in Canada and the USA have struggled with issues related to alcohol and drug testing of mothers and infants. There is some regional variation in policy in Canada and in the US. The guideline of the British Columbia Reproductive Care Program, an initiative of the Ministry of Health and the BC Medical Association, is that informed consent from the mother is required if an infant's hair, urine, or meconium are to be tested for alcohol and drug metabolites (111;250;258-261). If the clinician determines that a neonatal drug screen in absolutely necessary for care management then it can be obtained without maternal consent (111;250;258-261). However, there must be adequate justification in the medical record for such action. The rationale for obtaining a sample without consent may be inconsistent with legal precedent and the ethical position of the CMA.

2.3.3 Other Screening Programs and Consent

There are several universal screening programs related to maternal and child health currently in North America. Infants may undergo a hearing screen prior to discharge and parents may refuse the testing. Screening for phenylketonuria, a devastating genetic disorder that can be treated successfully through diet modification if

diagnosed early, is standard in Alberta. Parents are not always explicitly told that this test is performed and written informed consent is not sought but parents may opt out of testing if they wish. However, this is a disease for which there is an effective treatment and there is no social stigma attached to the diagnosis. The disease is not associated with parental behavior or lifestyle choices during pregnancy. Perhaps the most comparable universal screening program to screening for drugs and alcohol in meconium is that of Human Immunodeficiency Virus (HIV) testing. There is a social stigma attached to the disease, it is associated with a number of life style behaviors, and early interventions can make a difference in the long-term outcome for an infant (262;263).

The CMA and the Society of Obstetricians and Gynaecologists of Canada recommend offering HIV counseling and testing to all pregnant women, with informed consent. The approach to HIV screening in Canada varies by province (249;264-266). The first method is testing on a voluntary basis of pregnant women with risk factors for HIV. This is used in Prince Edward Island, Saskatchewan, and Ontario and approximately 51% of pregnant women in 1999 were tested (266). The second method is testing of all women on a voluntary basis, this is also known as “opt-in” testing (266). Clinicians counsel pregnant women about HIV transmission and offer testing. This is used in the Northwest Territories, Yukon, Manitoba, and Nova Scotia (266). Approximately 37% of pregnant women were tested in Manitoba using this method. Alberta utilizes the third consent strategy known as “opt-out” testing. Screening of pregnant woman is a routine part of a woman’s prenatal care and woman must explicitly reject the testing. The test is still theoretically voluntary and women are supposed to be counseled and give their informed consent; this may not always be the case. This strategy

is used in Newfoundland, Alberta, British Columbia and Quebec (266). The HIV testing lab form is separate from other blood work forms in Quebec and BC to make sure women provide consent. The "opt-out" method results in the highest proportion of pregnant women being tested. In Newfoundland 100% of pregnant women were tested in 2000, while only 80% of pregnant women in BC and 75% of pregnant women in Quebec were tested (266). There is a trend to an increasing proportion of women being tested in these regions and it is estimated that close to 98% of women will be tested using this method in the near future (264). An important component of any universal screening program is the voluntary nature of testing. A well-designed program should have high participation rates and should not damage the relationship between patient and clinician or the public health system and the community.

According to the World Health Organization's criteria for screening, a screening test or program should meet the following criteria: suitable tests should exist; the disease is important medically, socially, economically; the history of disease is understood and the population is identifiable; the test is acceptable to the population; the condition is recognizable at an early stage; there is an accepted and effective treatment for the condition; facilities for assessment, diagnosis and rehabilitation exist; interventions are acceptable to the population; the cost of screening is proportionate to the cost of caring for affected individuals; and screening programs are a continuing process (113;114;267). Currently, screening programs for alcohol and drug exposure would not meet the majority of these criteria (113). There are legal rulings on specimen collection from infants without parental informed consent in the United States of America (USA) that would prohibit the testing of all mothers in such a population (110;257). The issue is less

clear in Canada; however, as a first step, it would be desirable to understand under what conditions informed consent would be obtained (114).

2.3.4 Summary

Currently in Canada there is no defined policy on screening of meconium, hair or urine for drugs and alcohol or for the process of informed consent in such screening. The legal position is that informed consent is required in medical practice. Screening without consent may violate Canadian law and the individual's rights. If there is a desire to use alcohol and drug screening as a tool to target interventions and minimize health problems associated with prenatal alcohol and drug exposure in Canada, then factors that will improve willingness to consent should be identified.

Based on the information summarized in the literature review the MEC Study was conducted with the assumption that informed consent should be obtained prior to testing; and this could be accomplished with a well-designed and well implemented "opt-out" testing program. In addition, the consensus in the literature is that the results of drug testing should not be used to make decisions by Social Services or Child Welfare as to whether an infant should be apprehended however there appears to be a disconnect between the literature and clinical practice (249;252).

If jurisdictions in North America are interested in using alcohol and drug screening as a tool to target interventions and secondary disabilities associated with prenatal alcohol and drug exposure, then issues related to acceptability of the program and informed and willing consent to screening should be identified. Factors that will maximize the participation of women in a screening program need to be identified as

alcohol and drug use in pregnancy is an important public health problem. Methods of counseling during pregnancy and increasing women's control over their own health during pregnancy need to be identified. The goal then of any screening program is to maximize informed consent through education of all women of the potential benefits.

2.3.5 Theoretical Model – Women's Willingness to Consent

Given the position that informed consent is an absolute requirement in a universal screening program that has social and quasi-legal implications for the mother and infant, an understanding of factors that will improve willingness to provide informed consent is desirable. The Health Belief Model (HMB) is an appropriate theoretical model to better understand what influences a woman's willingness to consent and is increasingly used to understand lifestyle behaviors which require change (268;269). The HMB was originally used in an attempt to understand and explain an individuals acceptance of disease prevention and screening tests for the detection of asymptomatic disease (268;269). The four main components of the HMB are individual perceptions including perceived susceptibility, perceived severity, perceived benefits and perceived barriers. The likelihood of action which could be described as the perceived benefit of action minus barriers to action is influenced by cues to action and modifying factors. Meta-analysis has identified that the 4 components of the HBM are predictors of health behavior with perceived barriers being the most predictive (270).

The HMB can be applied to explain women's health behavior in the context of prenatal alcohol and drug use and identify the influence of modifying factors, individual perceptions, and cues to action on the likelihood of consenting to alcohol and drug

screening of their infant's meconium. The key components of the HMB and the likelihood of action, or in this case consenting, are perceived susceptibility and perceived severity of deficits associated with alcohol and drug use in pregnancy, perceived threat of deficits, perceived benefits of screening and early detection, cues to action, modifying factors, and perceived barriers to screening (268;269). See Figure 2.1 for a HBM that has been modified for willingness to consent to alcohol and drug screening.

Many pregnant women want to strive for a healthy pregnancy and healthy baby (271). However, through her behavior, a woman may harm her fetus (271). There are many social and other factors that may interrupt her intentions. The perceived susceptibility and severity (e.g., medical and social consequences) of disease will depend on education, age, understanding of the effects of the use of drugs on alcohol on the fetus, and peer group. Together, perceived sensitivity and susceptibility make up the perceived threat. The perceived threat of disease is also influenced by media, warnings on alcohol bottles, and clinician counselling. However, many members of society, including physicians, feel it is still acceptable to drink during pregnancy (188;272;273). In addition, it is not illegal to drink during pregnancy so this may not be seen as a "threat" to health. The perceived benefits of screening are not well known by the public; however, these include access to the best care possible for a child and interventions to minimise potential deficits or developmental delays. In the literature, perceived barriers are a major factor in determining the likelihood of consenting to screening (274). Barriers to consent for woman may include shame, guilt, denial of the problem, stigma associated with alcohol and drug use during pregnancy, fear of losing their children, lack of child care, and lack of accessible treatment (267).

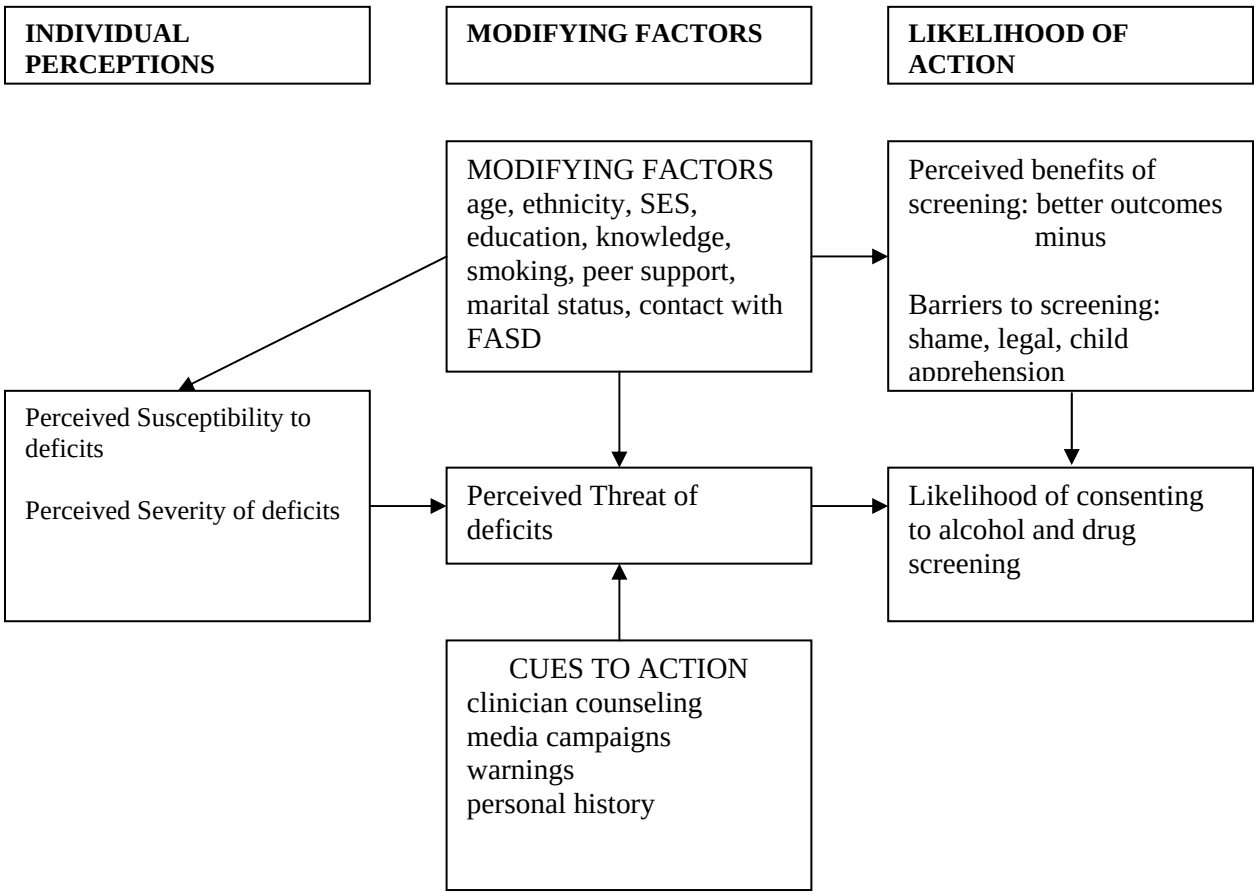


Figure 2.1. The Health Belief Model as predictor of health behavior in willingness to consent to alcohol and drug screen of an infant's meconium

In this figure "deficits" is used as an abbreviation for deficits associated with prenatal alcohol and drug exposure. Adapted from Rosenstock et al (268).

Chapter Three: Methods

This thesis examines questions related to alcohol and drug biomarker screening using three linked and overlapping studies. A prospective cohort was assembled to examine the association between maternal report of alcohol use and level of FAEE in meconium. The subjects from the cohort were then followed up at two years of age to examine the association between level of biomarker and child development. During the same timeframe as the prospective cohort study a cross-sectional survey was conducted in the source population for the prospective cohort study to identify under what conditions women would consent to alcohol and drug screening of their newborns.

3.1 Association between Maternal Self-Report and Concentration of Biomarker in Meconium

3.1.1 Study Design

This prospective population-based cohort study was conducted between September 2002 and August 2005 and was embedded in a prospective randomized controlled trial of pregnancy support, the Community Perinatal Care (CPC) Study which enrolled approximately 1500 women attending three maternity clinics in the Calgary Health Region (CHR). Pregnant women who sought services provided by family physicians at participating Calgary maternity clinics were invited to participate in the primary study. Women were excluded from the meconium sub-study if they were under the age of 18, lived outside the CHR, were not pregnant, could not communicate with study interviewers in English, or had a stillbirth or miscarriage. Subjects excluded from analysis if there was no meconium sample collected due to transfer or early discharge of

infant, the specimen was lost or not collected by mothers, or if there was insufficient meconium sample collected (less than 2.0 grams). Every effort was made to ensure that adequate samples were collected from all enrolled subjects. This included frequent faxed reminders and visits to the labour and delivery and post-partum units by research assistants.

3.1.1.1 Subject Recruitment

Receptionists, Office Managers and on-site research assistants at the clinics were asked to inform new patients about the study. Contact information for all women scheduled to attend prenatal clinics was provided to a research assistant and entered into a Computer Assisted Telephone Interviewing (CATI) System. Trained telephone interviewers contacted patients, provided information about the study, and invited patients to participate. After obtaining informed consent the women completed a baseline interview and questionnaire. Following a second study questionnaire at 32-34 weeks, pregnant women were contacted to discuss their potential participation in a study that examined lifestyle and substance use during pregnancy and levels of biomarkers in meconium. The women were told that results of all biomarker analyses would be kept confidential and would not become part of any medical record. However, the results of the meconium analysis would be linked to the source study dataset and data from the prenatal record. Only the study investigators had access to identifying information and all data were kept in a secure location. Verbal consent was obtained as an extension of the written consent that women had already provided for the CPC study (Appendix A). An information package and a meconium sample collection kit were sent to participants. The

study package included a copy of the verbal consent, an information sheet, and a study identification card that subjects presented to their nurses when admitted to a labor and delivery unit in the Calgary Health Region (Appendix A).

3.1.2 Data Collection

Study participants completed 3 telephone interviews over the study period (first trimester, 32 to 34 weeks gestation, and 8 weeks post delivery). Three questionnaires were developed to address the CPC study objectives and were based on input from focus groups and consultations with physicians, nurses, epidemiologists, program developers, psychologists, and published literature. The questionnaires each took 30 to 40 minutes to complete and included questions about resource utilization, demographics, lifestyle, psychosocial health, network orientation and history of abuse and neglect. The following tools were included: Kellner Symptom Questionnaire, T-ACE, Rosenberg Self Esteem , McCubbin Social Support Index, Woman Abuse Screening Tool (WAST), Edinburgh Postnatal Depression Scale and Vaux Network Orientation Scale, which assesses a person's willingness to maintain, nurture, or use the social supports that she has (89;275-282). Questions were also taken from the Canadian National Population Health Survey (NPHS) (283). The questionnaires were pilot tested, revised and coded for a Computer Assisted Telephone Interviewing (CATI) system (see Appendix B for a sample CPC questionnaire). Linkage to the Alberta Perinatal Health Program Dataset was performed by personal health number, maternal date of birth and child date of birth to obtain information on antenatal care related to alcohol use documentation in the prenatal record and opiate administration during labor as well as birth outcomes (e.g., meconium

staining, Apgar scores). Interview data were maintained in a password protected CATI system and Microsoft Access Database and extracted into a Statistical Package for the Social Sciences (SPSS version 14.0) dataset (284).

All materials and data pertaining to the study were secured in offices at Alberta Children's Hospital (ACH). All files were secured and locked in a file cabinet. Confidentiality was maintained throughout the study. Entry of meconium analysis data from the analytical laboratory was in duplicate by research assistants trained in strategies for data entry to minimize data entry errors. The study participants were identified exclusively by study number. Data were linked from CPC study questionnaires and meconium analysis.

3.1.2.1 Alcohol Intake, Illegal Drug Use, and Food Intake

The specific questions used to assess alcohol and food intake prior to, during and following pregnancy were taken from the National Population Health Survey and have been validated for obtaining food, alcohol and drug use histories in the Canadian population (283). Measures of average amount (oz) of absolute alcohol consumed per day, absolute alcohol consumed per week, and average amount (oz) of absolute alcohol consumed per actual drinking days were calculated based on reported frequency of intake and amount of alcohol consumed per occasion. Frequency of binge episodes was based on self-reported occasions in which 5 or more drinks were consumed. Preconception drinking and alcohol use prior to pregnancy recognition were also determined by the same methods. The T-ACE was also used to identify women at risk for drinking during pregnancy. A positive T-ACE score (defined as a score 2 or greater) is believed to identify the majority of women who drink heavily during pregnancy (89).

- T-tolerance – How many drinks does it take to make you to feel high? A response of greater than 2 drinks = 2 points with 2 drinks or less=0;
- A-Annoyed – Have people annoyed you by criticizing your drinking? Yes=1 point;
- C-Cut down – Have you felt that you ought to Cut down on your drinking? Yes=1 point; and
- E-Eye opener – Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? Yes=1 point.

3.1.2.2 Meconium Collection and Analysis

Study participants took their meconium sample collection kits to hospital with them at onset of labor and identified themselves to their nurses as study participants. Spare sample collection packages were placed on all labor and delivery units. Packages included labeled diapers, which allowed nurses to identify study infants, hypoallergenic diaper liners, and sample vials prelabeled with a subject's unique identifier. A list of enrolled study subjects was kept at labor and delivery units, postpartum units and special care nurseries to aid in subject identification. These lists were updated on weekly basis. Once meconium was passed it was transferred to the sample vial from the diaper. If necessary, meconium was collected from several diapers until at least 2.0 grams was obtained. The vial was submitted to the hospital clinical laboratory for storage at –80°C until analysis. If an infant was discharged home prior to passage of meconium, families were asked to collect the sample at home and keep it in their freezer until it was picked up by a study team member. Samples were shipped on dry ice to United States Drug

Testing Laboratories, Inc. (Des Plaines, IL, USA) via courier to maintain samples in a frozen state as requested by testing laboratory.

Based on an evaluation of the literature and all available testing options, a comprehensive test panel used to detect fetal substance exposure was identified. This test panel measures fatty acid ethyl ester concentrations to ascertain fetal alcohol exposure by GC/MS technology and uses immunoassay and GC/MS for the detection and confirmation of drugs of abuse such as cocaine, opiates, amphetamines, opiates, marijuana, and phencyclidine (96-98).

Meconium analysis for metabolites of alcohol and drug use (e.g., fatty acid ethyl esters, cocaine, opiates, amphetamines, cannabinoids, and phencyclidine) was based on methods developed and described previously by United States Drug Testing Laboratories, Inc, a forensic drug testing company laboratory accredited in routine chemistry, urinalysis and toxicology by the United States Drug Enforcement Agency, the College of American Pathologists, the Drug and Alcohol Testing Industry Association and the Centers for Medicare & Medicaid Services Clinical Laboratory Improvement Amendments (96-98).

The laboratory performing the analysis was blind to all maternal characteristics, i.e., maternal self-report, T-ACE score, patient identifiers, maternal age. Drug metabolite analysis involved a fluorescence polarization immunoassay screen with gas chromatography/mass spectroscopy confirmation (96). FAEE analysis involved extraction followed by quantification by gas chromatography/mass spectrometry. Comparison to the retention times and peak sizes of authentic deuterated standards of lauric, myristic, palmitoleic, palmitic, linoleic, oleic, linolenic, stearic, arachidonic acid

ethyl esters was used to determine the amounts of specific FAEE in the meconium. Total FAEE amounts in each sample in ng/g of meconium were based on the combination of palmitoleic, palmitic, linoleic, oleic, linolenic, stearic and arachidonic acid ethyl esters. Limits of detection (Table 4.3) were used to identify samples as positive or negative for a given FAEE.

The Standards for Reporting of Diagnostic Accuracy (STARD) criteria for evaluation of diagnostic tests were followed as closely as possible with this study protocol (285;286). However, given that there is no 'gold standard' for alcohol exposure these criteria are used to maximize the quality of reporting of results rather than imply that FAEE analysis is a diagnostic test

3.1.3 Statistical Analysis

Statistical analyses were conducted in Statistical Package for the Social Sciences (SPSS version 14.0) and STATA version 9.0 (284;287). Bivariate analysis was used to identify prevalence of maternal alcohol and drug use by strata of perinatal and maternal characteristics. Differences between positive and negative groups were analyzed with Fisher's Exact 2-sided test for categorical variables. The independent samples t-test was used to assess continuous data after logarithmic transformation of the data when appropriate. An alpha level of 0.05 or less was considered statistically significant for bivariate analyses and was also the cut off criteria for considering variables for logistic regression models in conjunction with other theoretical considerations. Multiple comparison adjustments were not used due to the exploratory nature of this study.

Scatterplots were created to examine the associations between self-reported alcohol use and all species of meconium FAEEs. Statistical analyses were performed using total FAEE concentration thresholds in meconium above the limit of detection (LOD), 50 ng/g, 500 ng/g, 10,000ng/g, any oleic acid and any linoleic acid based on thresholds reported in the literature (92-94;96-98;107-109;235;236).

3.1.4 Sample Size

Sample size was calculated with a 2-sided alpha of 0.05 to have 90% power to detect a difference of 50% positive screens for FAEEs in the infants of women who do not report alcohol use and 72% positive screens for FAEEs in the infants of women who do report alcohol use based on the worst-case sensitivity and specificity information of FAEE analysis presented by Bearer *et al* (93). Based on sample size calculation a recruitment goal of 111 women who reported alcohol consumption and 111 with no reported alcohol consumption was set. Alcohol use was identified by T-ACE score and self-reported alcohol consumption on the study intake questionnaire.

3.2 Biomarker Level and Child Development

3.2.1 Study Design

This prospective population-based cohort study was conducted between November 2004 and May 2007 as a continuation of the Meconium Alcohol and Drug Screening sub-study (MEC Study) of the Community Perinatal Care (CPC) study. The study examined the association between FAEE concentration in meconium and child motor, mental and behavioral development at 2 years of age as assessed by standardized assessments, developmental paediatrician and standardized parental-report questionnaires.

3.2.2 Subject Identification and Approach

Women had previously completed extensive telephone surveys at 10-12 weeks and 30-32 weeks of pregnancy and at 10 weeks postpartum and provided a meconium sample for drug and alcohol metabolite analysis. At the time of recruitment into the MEC Study subjects were told about the planned follow up study and subjects were asked if they could be contacted to participate in this research.

In total 132 infants were recruited with 32 infants with elevated FAEE concentrations above the limit of detection (LOD) of 16 ng/g and 100 infants with concentrations of FAEE below the LOD were recruited from the MEC Study. An experienced interviewer and recruiter contacted the women by telephone to tell them about the project. The women were invited to participate in a prospective cohort study examining the link between biomarkers in meconium and child motor, mental, and behavioral development. The women were told that some infants had higher levels while

others had lower levels of biomarkers and at this point researchers in this area do not know what the level of biomarker might signify for child development. The women were told that results of all FAEE analyses were confidential and would not become part of any medical record. See Appendix A for a copy of the enrolment script and consent form. An information package was sent to consenting women and included a description of the project and a copy of the consent form that women were asked to sign at the time of their first follow-up visit. Women were offered compensation for expenses incurred as a result of participation such as parking, transportation, and childcare costs.

3.2.2.1 Inclusion Criteria

Participants in the MEC Study who lived within one hour of Calgary and who could speak, read, and write English and who provided written consent.

3.2.2.2 Exclusion Criteria

Reasons for exclusion included no or inadequate meconium or refusal to be approached for future studies at time of enrolment in the MEC Study. Children with significant medical histories that may explain developmental delay were included in the study but excluded from some analyses.

3.2.3 Testing at Follow-up

Many global tests have been developed to assess child cognitive and motor development. However, prenatal alcohol exposure effects are difficult to assess in the 24 month age range and global developmental tests may not be sensitive enough to detect a

difference between exposed and unexposed groups. The lower the level of exposure, the more sensitive and specific the tests that must be used (16). For this reason a number of tests were used to assess several domains.

At the 24-month follow up visit children were assessed using several psychological tools, had an examination with a developmental pediatrician, and completed several standardized parental-report questionnaires. All assessments and interviews were performed by individuals who were masked to the FAEE level in the meconium of the child. Standardized data collection sheets were developed with input from team members (see Appendix B for the Child History Form). The testing routine and questionnaires were pilot tested on 4 subjects and revised. The follow up assessment was typically broken into 2 visits. The first visit included the administration of the Bayley Scales of Infant Development, 2nd Edition (BSID-II) to children and the Wechsler Abbreviated Screening Instrument (WASI) to mothers while the second visit included the assessment by the developmental paediatrician.

Domains that were assessed included child mental, motor, and behavioral/social development, temperament, adaptive behavior, socialization, maternal intelligence, home environment, family interaction, and parental satisfaction. The tests included the BSID-II, Nurturance Interview, the Home Screening Questionnaire (HSQ), Family Assessment Device (FAD), Toddler Temperament Scale (TTS), Temperament and Adaptive Behavior Scale (TABS), ABAS, Child Behavior Checklist (CBCL), Parenting Satisfaction Scale (PSS), Ages and Stages Questionnaire (ASQ), Nippissing District Developmental Screen (NDDS) and Wechsler Abbreviated Screening Instrument. See Appendix B for a table of

tests used, who administered them and approximate time involved. The scales used are copyrighted material and are therefore not attached in an appendix.

3.2.3.1 Developmental Paediatrics

The assessment with the developmental pediatrician included a screening history, physical examination, dysmorphic facial feature examination, growth characteristics (e.g., height, weight, head circumference), and the Nurturance Inventory. Percentile values for height, weight, and head circumference were determined using Centers for Disease Control normative values and growth charts (288).Clinical, physical, psychological, behavioral or psychosocial manifestations at time of follow-up triggered a clinical or psychosocial investigation as warranted. See Appendix B for the Pediatrician Data Collection Form.

3.2.3.2 Psychological Tests

All psychological tests (e.g., BSID-II, WASI) were administered and scored by psychologists or psychologist assistants trained in their use. At a minimum, they were Masters level psychology students who were supervised by an experienced certified psychologist team member. A brief, descriptive report was prepared by team psychologist based on the standardized assessments and sent to participants (Appendix B). Each of the standardized tools is described below.

3.2.3.2.1 Bayley Scales of Infant Development-II (BSID-II)

The BSID-II is an individually administered tool to identify children with cognitive or motor delay (289). The BSID-II is a measure of mental and motor development. The

BSID-II was normed on a stratified random sample of 1,700 children (850 boys and 850 girls) aged one month to forty-two months. The sample was stratified to resemble the 1988 U.S. Census statistics on the variables of age, sex, region, race and ethnicity, and parental education for 17 regions in the US (289). The BSID-II yields 3 scales called the Mental Scale; the Motor Scale; and the Behavior Rating Scale. The Mental Scores are converted to a standard scale called the Motor Development Index (MDI). The MDI evaluates sensory-perceptual acuities, discrimination, vocalization, beginning verbal communication, mental mapping, language and mathematical concept formation, and object constancy memory. The Motor Scale assesses body control, large-muscle coordination, fine motor skills, and motor quality. The Motor Scores are converted to a standard scale called the Psychomotor Development Index (PDI). The Behavior Rating Scales supplements the MDI and Motor Scale and rates attention, test-taking behaviors, and emotional regulation (289).

The test is administered by a trained psychologist (or psychology student supervised by a licensed psychologist) and takes approximately 90 minutes to administer and score. The BSID-II can be used to identify relative strengths and weaknesses but it is not predictive of later childhood competence. Reliability coefficients for the Mental Scale range from 0.78 to 0.93. The test also reportedly has adequate short-term test-retest stability and interrater reliability. The test has interrater reliability of 0.89 to 0.93, test-retest reliability of 0.75-0.76 and has high clinical validity as it was developed with children at risk (e.g., preterm, Down syndrome) The BSID-II is not predictive of performance (0.2 to 0.3) on IQ tests at ages distant from the BSID-II assessment. However, it is a good assessment of current performance (289). It is considered the “gold

standard" in the literature for assessing global child development in this age range. In this study the BSID-II will serve as the primary outcome at 18 months as an assessment of mental and motor development.

3.2.3.2.2 Achenbach Child Behavior Checklist/1½-5 (CBCL/1½-5)

The CBCL/11/2-5 is a newly revised version of the Child Behavior Checklist/2-3 (290). It is a 99 item list of parents' ratings of their child's problems and disabilities, as well as what parents' are concerned about most with their child, and what are the best things about their child (290). The CBCL/11/2-5 was normed using a large national US sample of 700 children. The test assesses the following domains: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Attention Problems, & Aggressive Behavior, and Sleep. The test yields an Internalizing, Externalizing, and Total Problems score. The CBCL/11/2-5 profile of Diagnostics and Statistical Manual (DSM) oriented scales include Affective Problems, Anxiety Problems, Pervasive Developmental Problems, Attention Deficit/Hyperactivity Problems, & Oppositional Defiant Problems. The revised test also includes the Language Development Survey (LDS) which can be used to assess language delays for ages 18 to 36 months. The CBCL is considered the gold standard in the literature, is one of the most widely used assessment of behavior for children, and many recent studies of drug or alcohol exposure and outcome have used the CBCL. Subscales have good test-retest reliability (0.71 to 0.93), and interparental agreement (0.63) (290).

3.2.3.2.3 Temperament and Atypical Behavior Scale (TABS)

The TABS Assessment Tool is a 55 item caregiver completed checklist designed to measure child temperament and self-regulation in the domains of detached, underreactive, hyper-sensitive/active and dysregulated for children aged 11 to 71 months. The TABS is written at the 3rd Grade reading level and takes under 15 minutes to complete. It was developed with 200 children with atypical or undesirable behavior (e.g., FASD, ADHD, Autism Spectrum Disorders) and norm-referenced with a sample of over 600 normal children. The TABS is valid, reliable, and stable over time. It is clinically valid as it was developed with a sample of children with atypical behavior and has a split half reliability of .81 to .95 in children with disabilities (291). Stability coefficients over time are between .73 and .94 (291).

3.2.3.2.4 Carey Temperament Scale (TTS)

The Carey Temperament Scale that is applicable to this study is the Toddler Temperament Scale (TTS) (292;293). The TTS is a self-administered questionnaire of 97 items across nine domains that takes approximately 20 to 30 minutes to complete and 10 to 25 minutes to score. The scale is used to assess temperament of children to contribute to an understanding of behavior and behavior problems. A caregiver rates items based on observations and experience with the child. The TTS was standardized with a sample of 309 children from white, middle-class families. The instrument is reported to have high test-retest reliability (0.8), interrater reliability (0.81), acceptable internal consistency, and concurrent validity (292;293).

3.2.3.2.5 Home Screening Questionnaire (HSQ)

The HSQ in the survey form of the Home Observation for Measurement of the Environment (HOME) Inventory (197). It is designed to assess the family environment, parent-child relationships, and factors which may impact normal child development for children 0 to 6. The HSQ is self-administered in 15 to 20 minutes and scored in 5 minutes. The instrument for younger children has thirty items and a toy list. The HSQ was normed on a population of 1500 lower SES parents that were also administered the HOME Inventory. Between 81% and 86% of items of concern identified by the HOME Inventory were also identified by the HSQ. There is high correlation between 12-month HOME score and psychological measures and school performance 5 to 7 years later. The HSQ has internal reliability of 0.74 and test-retest reliability after a 2-week interval of 0.62. (197).

3.2.3.2.6 Parenting Satisfaction Scale (PSS)

The Parenting Satisfaction Scale is self-administered 4-page, 45-item questionnaire that assesses parent's attitudes in the domains of satisfaction with spouse/ex-spouse parenting performance, satisfaction with the parent-child relationship, and satisfaction with parenting performance (294). Parenting satisfaction appears to be related to behavioral outcomes (294). Each of the domains contains 15 items and the whole scale can be completed in 20 minutes. The PPS's internal consistency, estimated using Cronbach's alpha, was from 0.82 to 0.96 on the 3 subscales. Parenting satisfaction has been correlated with children's social and academic performance (294).

3.2.3.2.7 Wechsler Abbreviated Screening Instrument (WASI)

The WASI is a rapid measure of intelligence that was developed with a normative sample of 2,245 children and adults, aged 6 to 89 (295). The four-subtest WASI will be administered to caregivers in this study to derive a rapid assessment of IQ. The four-subtest WASI yields a Full Scale IQ that is consistent with other Wechsler tests with a mean of 100, a standard deviation of 15, and a range from 50 to 160. The WASI has good test-retest reliability for adults ranging from 0.79 to 0.90 and split-half reliability from 0.92 to 0.98. The WASI also has considerable validity with good correlation with Wechsler comprehensive test subscales and IQs (0.76 to 0.92) (295).

3.2.3.2.8 Family Assessment Device (FAD)

The Family Assessment Device (FAD) is a 60-item self-administered questionnaire for those 12 years of age and older that takes approximately 20 minutes to complete. The questionnaire was developed to assess healthy and unhealthy family functioning through seven subscales: problem-solving, communication, role, affective responsiveness, affective involvement, behavior control and general functioning. Internal reliability and validity have been demonstrated with Cronbach's alpha values in the 0.74 to 0.92 range (296;297). The test also has adequate test-retest reliability, low correlation with social desirability, and is moderately correlated with other self-report measures of family functioning (296;297).

3.2.3.3 Questionnaires

A child history form and standardized questionnaires, i.e., ABAS, TABS, CBCL, FAD, PSS, and HSQ were sent to subjects in advance of their follow up visit. These were used to collect information on variables that may confound the relationship between FAEE concentration and child development. At the time of the follow-up visit the study coordinator ensured that the questionnaires were completed. See Appendix B for a copy of the Child History Form.

3.2.4 Strategies to minimize loss to follow-up

It was crucial that a high level of follow-up be maintained with this study. Costs to the subjects were minimized by paying for parking or transportation to the testing site for follow-up and provision of a meal voucher on the day of testing as subjects spent several hours at Alberta Children's Hospital. In addition, the siblings of study subjects were cared for by a certified childcare worker on the day of follow-up assessments, or the study reimbursed subjects for childcare costs. Strategies used to maintain the interest of subjects in participating in follow up studies were described by Streissguth *et al* and include newsletters about the project, Mother's Day cards, and a fun and informal environment for developmental testing (298). In addition, at the completion of each testing cycle the children were given a small age-appropriate toy and a book as a gift to thank them for participating in the study. These strategies helped to ensure that the study had the most recent contact information for subjects and that mothers and children enjoyed the experience.

3.2.5 Data Handling

All materials and data pertaining to the study were secured in locked filing cabinets in research offices at Alberta Children's Hospital. Confidentiality was maintained throughout the study. Data were entered in duplicate using Statistical Packages for the Social Sciences (SPSS) (284). Computer files were password protected. Data were imported into Intercooled STATA 9.0 (College Station, Texas) for analysis (287).

3.2.6 Statistical Analysis

All statistical analyses were performed with Intercooled STATA Version 9.0 (College Station, Texas) (287). All tests were two-sided (where applicable) and significance was defined as p-value <0.05. Multiple comparison adjustments were not used due to the exploratory nature of this study. Univariate descriptive statistics were used to identify potential data entry errors, and characterize subjects. Test scores and maternal and child variables were examined in terms of mean, median, range, proportion, standard deviation, skewness, and quartiles. Histograms, stem-leaf, and box plots were generated to evaluate assumptions of normality and to identify outlying values. Transformations of variables were performed as required. Bivariate analysis was used to compare test scores (e.g., BSID-II scales) by strata of FAEE levels, and perinatal and maternal characteristics. The categorical demographic characteristics of women and infants in the positive and negative groups were compared by χ^2 analyses or Fisher's exact test where appropriate. Continuous variables were compared between groups using Student's *t* test (two-sided). Spearman correlation was used to assess correlation between

BSID-II outcomes and FAEE. FAEE and scores on the BSID-II, ABAS, TABS and CBCL were examined as continuous and categorical variables.

Hypothesis generating multivariate linear and logistic regression models were developed with data obtained from the comprehensive CPC dataset, which included responses from CPC questionnaires 1, 2, and 3 and account for self-reported alcohol use during pregnancy. The dependent variables in this study were the Mental and Motor Development Indices of the BSID-II. Independent variables, including potential confounders or effect modifiers of the association between FAEE concentration and development identified in the review of the literature that were examined included maternal self-report of alcohol and drug use, T-ACE questionnaire score, maternal age, maternal intelligence, gestational age, maternal education, maternal history of depression, self-reported income, marital status, food and housing security, maternal cigarette use during and after pregnancy, parenting satisfaction, and maternal history of abuse. Models of variables in the domains of maternal characteristics, mental health, lifestyle, psychosocial factors, drug and alcohol use, and child characteristics were constructed. As infant birth characteristics like birth weight, length and head circumference can be a result of alcohol exposure (e.g., potentially in the casual pathway) these were assessed as possible mediating variables of the association between outcomes of interest and FAEEs. Infant birth characteristics were entered into models after all other variables. Variables were included in the models if they were significantly associated with the outcome at $p<0.2$ in preliminary regression analysis. Variables significant in domain models were included in a model of all variables and then removed in a backwards stepwise fashion to yield a parsimonious model. The presence of interaction and confounding was assessed

using standard statistical techniques. Adjusted odds ratios and 95% confidence intervals were calculated.

3.2.7 Sample Size

Thirty-two infants with elevated FAEE concentrations in meconium and 100 infants with FAEE concentrations below the limit of detection were recruited for this study. Given that a limited number of subjects with elevated FAEE concentrations were identified all subjects with an FAEE concentration above the LOD were contacted for follow-up. The values from the FAEE analysis of the first 150 subjects recruited were used to calculate an estimated variance for the scores that might be seen with the 30 FAEE subjects at follow up. This estimated variance was used in combination with the population normative value for the BSID-II Mental and Psychomotor Development Indices, mean 100 and standard deviation of 15, and a 3 to 1 case-control ratio to calculate a power curve (Figure 3.1) for the correlation between BSID-II and FAEE amount (289). This study had 80% power to detect a correlation of 0.22.

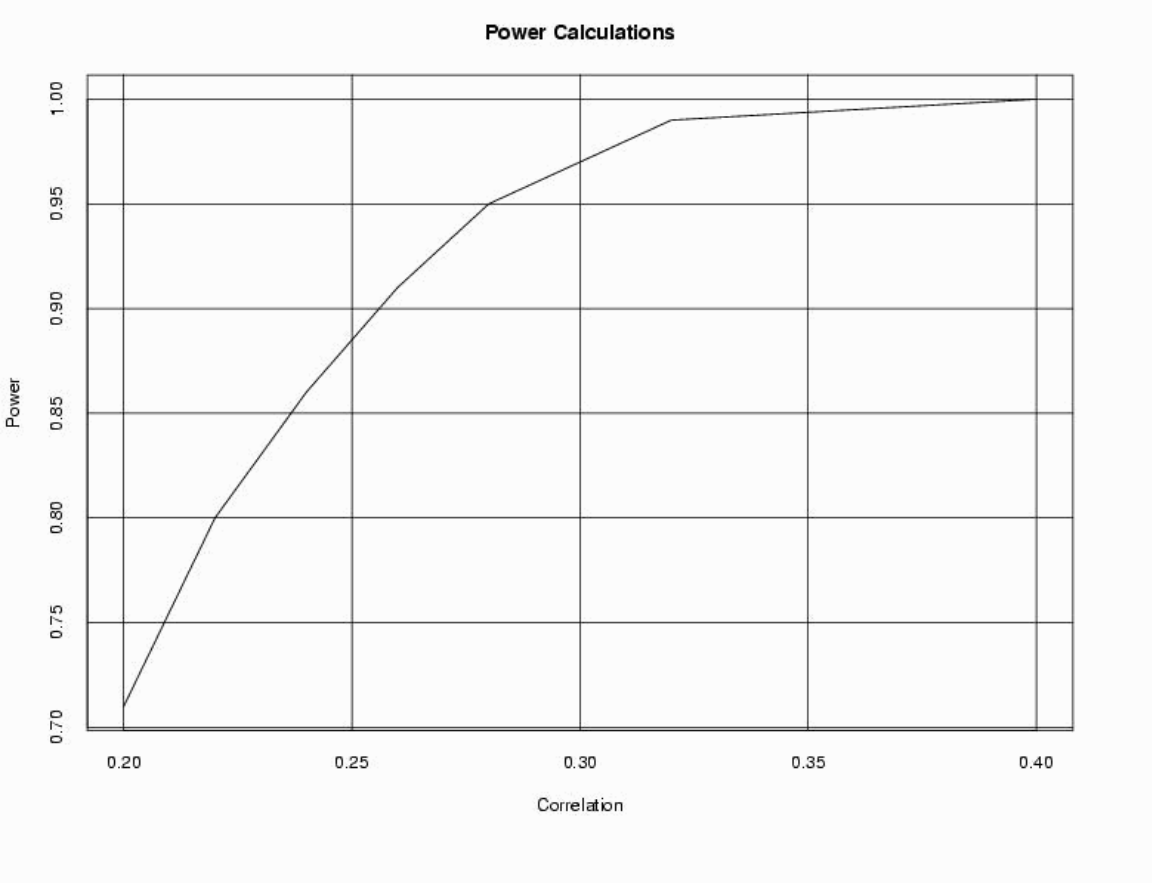


Figure 3.1. Power curve for the correlation between Bayley Scales of Infant Development, Second Edition Mental and Psychomotor Development Indices and amount of fatty acid ethyl esters in meconium.

3.3 Maternal Willingness to Consent

3.3.1 Study Design Overview

This study used focus groups and a cross-sectional survey to address the research questions. More specifically, focus groups were convened to obtain insight on women's opinions, attitudes, and beliefs about newborn alcohol and drug screening, as well as for hypothesis generation and to develop a cross-sectional survey that was administered to a large audience in the Calgary Health Region (CHR).

3.3.2 Focus Groups

3.3.2.1 Subject Identification and Approach

Women approached to participate in this study were from two groups. Women considered low-risk were recruited from prenatal classes and low risk maternity clinics. High-risk women were recruited from the Calgary Urban Projects Society (CUPS) and CUPS One World. Low-risk and high-risk in this context refers to risk of alcohol and drug use in pregnancy. Participants were carefully recruited by trained research assistants on-site to ensure a range of perceptions and experiences. See Appendix A for copies of the enrolment script and consent form. Women were offered compensation for their expenses incurred as a result of participation such as parking, transportation, and childcare costs. Participants were also offered food and refreshments at the time of the focus group and at the end of the focus group women were given a coupon for $20 of groceries.

3.3.2.2 Data Collection

Focus groups were composed of 5 to 15 participants, a facilitator, and a research assistant. Open-ended questions on a semi-structured interview guide were used for the focus group discussion (See Appendix B). Questions were organized from more general questions about pregnancy, women's knowledge of risk associated with alcohol and drug use during pregnancy, and challenges during pregnancy for women in the community to more specific questions about alcohol and drug testing of newborns and the reasons why a woman would or would not want such testing. Participants provided informed consent, were fluent in English, were pregnant or had delivered an infant in the previous year, and were greater than 18 years of age.

3.3.2.3 Focus Group Data Analysis

Transcripts of focus groups were prepared and analyzed from audio recordings. Tapes and transcripts of focus groups were stored in secure offices at Alberta Children's Hospital. The data were coded by 3 investigators using inductive coding; codes were developed as the data were examined. Codes were revised and refined and the data summarized at a consensus meeting. Words, phrases, word categories and codes were enumerated and examined for relationships within and across focus groups using the elements of the HBM; perceived susceptibility, severity, threat, benefits, and barriers (268;269). The analysis of these data was used for hypothesis generation and questionnaire development. Language and themes from the focus groups were consistent with those used in the questionnaires.

3.3.2.4 Cross-Sectional Survey Development

The questionnaire was framed around the HBM elements of perceived susceptibility, severity, threat, benefits, and barriers (268;269). Questionnaire wording was kept as similar as possible to that used by focus group participants. Several scenarios were developed with different consequences for a positive drug or alcohol screen. Women were asked to indicate their agreement with screening given a potential outcome on a 5-point Likert scale (i.e., strongly agree to strongly disagree). In addition, demographic and perinatal variables were collected for subsequent analysis. Women were asked about alcohol use during pregnancy and were administered the T-ACE, a standardized alcohol use screening questionnaire. See Appendix B for a copy of the questionnaire. The survey was administered to 5 women who took part in the focus groups and revised based on their feedback. The survey was piloted on 40 women on postpartum units then revised.

3.3.3 Cross-Sectional Survey

The survey was administered to all eligible, consenting postpartum women fluent in English and admitted to one of the three postpartum units in the Calgary Health Region over a 4-month period (July 2003 to October 2003). Women were identified from postpartum unit admission logs and approached to participate in the survey. *Exclusion criteria*: under 18 years of age; language barriers; protective custody; infant in process of apprehension by Children's Services; discharged prior to being approached to participate; and serious maternal or neonatal complications. Written informed consent was obtained

and the twenty minute questionnaire was administered by a research assistant. Questionnaires were anonymous.

3.3.4 Statistical Analysis

Data were entered and analyzed in SPSS 14.0 (284). All tests were two-sided and significance was defined as p-value <0.05. Univariate descriptive statistics were used to describe participants. Bivariate analysis was used to help understand willingness to consent by self-reported alcohol use, demographic and lifestyle characteristics. Categorical variables were compared using chi square tests and continuous variables were compared by Student's *t*-test. An alpha level of 0.05 or less was considered statistically significant and was also the cut off for considering variables for logistic regression models. A logistic regression model was created using forward selection method to describe the independent characteristics of women who would consent compared to those who would not consent. Confounding and interaction variables were evaluated. Variables were entered into the model building process in the following order: lifestyle, information women would need, likely outcome of a screening program and demographic predictors. Adjusted odds ratios and 95% confidence intervals were calculated.

3.3.5 Sample Size

It was hypothesized that there would be differences in willingness to consent based on self-reported alcohol use. Using an estimate of a difference in willingness to consent of 15% between those who report alcohol use and those who do not, sample size

was calculated at 134 per group with a 2-sided alpha of 0.05 to have 80% power. Sample size was designed to be large enough to allow for stratified analysis and to control for potentially confounding factors.

3.4 Ethics Approval

All components of this work received ethics approval from the Conjoint Health Research Ethics Board of the University of Calgary. Copies of ethics approvals are presented in Appendix A. Approval of the thesis proposal by the supervisory committee is presented and acted as scientific review and approval (Appendix A).

Chapter Four: Results

4.1 Association Between Maternal Self-Report and Concentration of Biomarker in Meconium

4.1.1 Recruitment and Participation

A flowchart of recruitment, participation and sample collection is presented in Figure 4.1. In total, 644 pregnant women were approached to participate in the study. Of those approached, 460 women (71.4%) were eligible, 344 (74.8%) participated and 238 (70%) collected a valid sample.

Compared to women who participated in the study, women who did not participate were more likely to be of non-Caucasian ethnicity which is consistent with a group that has difficulty accessing prenatal care and services (Tables 4.1 and 4.2). In addition, women who participated but did not collect a sample were more likely to have non-Caucasian ethnicity, a past history of being unemployed when wanting to work; and a past history of suicidal thoughts or attempts.

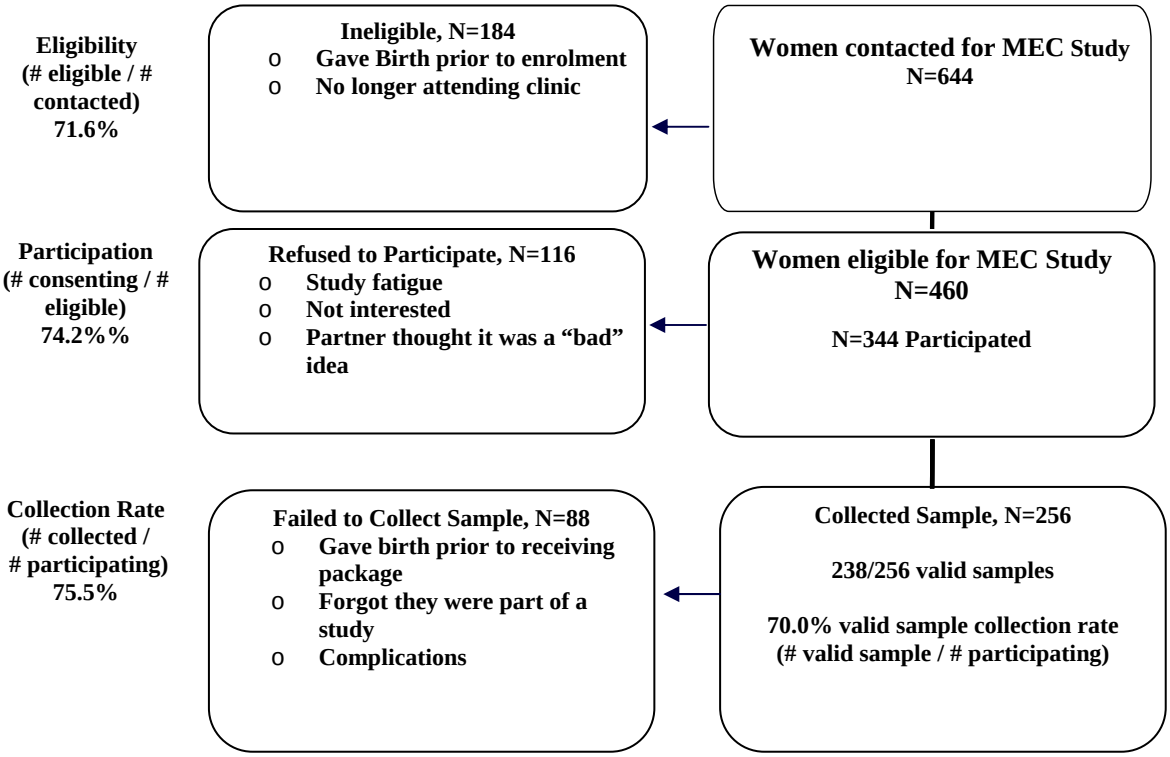


Figure 4.1. Study flowchart of recruitment of women participating or approached to participate in the Meconium Screening Study

Table 4.1. Sociodemographic and lifestyle characteristics of women who completed the Community Perinatal Care and Meconium Screening Studies compared to women who did not participate in the Meconium Screening Study or those who failed to collect a sample

Characteristic	Completed CPC Study	MEC Study					
		Participant *	Non-Participant **	p value	Collected Sample	No Sample	p value
	N=1561 n (%)	N=211 n (%)	N=82 n (%)	exact	N=256 n (%)	N=83 n (%)	exact
Maternal age (yr)	29.2 sd (5.0)	**30.7 sd (4.8)**	**29.3 sd (4.8)**	**0.025**	31.3 sd (4.5)	30.7 (4.6)	0.276
Not married	112 (7.2)	11 (5.2)	6 (7.3)	0.329	10 (3.9)	4 (6.1)	0.319
Have spouse/ partner	1533 (98.2)	206 (97.6)	82 (100.0)	0.191	253 (99.2)	63 (95.5)	0.061
Non-Caucasian	378 (24.2)	**37 (17.5)**	**27 (32.9)**	**0.007**	**31 (12.2)**	**16 (24.2)**	**0.014**
Education				0.289			0.785
< High school	116 (7.5)	10 (4.7)	8 (9.9)		9 (3.5)	3 (4.6)	
High school	279 (17.9)	34 (16.1)	12 (14.8)		30 (11.6)	9 (13.6)	
Post-secondary	1162 (74.6)	167 (79.2)	61 (75.3)		216 (84.7)	54 (81.8)	
Income							
< $40,000/yr	109 (9.0)	37 (18.2)	18 (24.7)	0.156	33 (13.5)	11 (17.7)	0.255
Food bank use*	67 (4.3)	6 (2.8)	5 (6.1)	0.164	6 (2.3)	1 (1.5)	0.560
Occupation							
Homemaker*	370 (23.7)	45 (21.3)	35 (30.5)	0.069	62 (24.3)	16 (24.2)	0.565
Daily Smoking*	298 (19.1)	46 (21.8)	21 (25.3)	0.356	40 (15.5)	13 (17.9)	0.623
Alcohol*				0.146			0.873
<1 time/month	1349 (86.6)	161 (76.3)	66 (79.5)		189 (73.8)	65 (74.7)	
Several/month	170 (10.9)	45 (21.3)	12 (14.5)		60 (23.5)	19 (21.8)	
Daily	38 (2.4)	5 (2.4)	5 (6.0)		7 (2.7)	3 (3.5)	
Drug Use**	134 (8.6)	20 (9.5)	6 (7.3)	0.653	20 (7.8)	6 (9.1)	0.800
Exercise						13 (19.7)	
≥3 times/wk	564 (36.1)	33 (15.6)	21 (25.6)	0.153	44 (17.2)	34 (51.5)	0.621
1-2.9 times/wk	729 (46.7)	106 (50.2)	36 (43.9)		122 (47.8)	19 (28.8)	
<1 time/wk	268 (17.2)	72 (34.1)	25 (30.5)		89 (34.9)		

*Only considering women who were the part of the main CPC cohort.

**Within the 12 months prior to pregnancy.

Table 4.2. History of life events of women who completed the Community Perinatal Care and Meconium Screening Studies compared to women who did not participate in the Meconium Screening Study or those who failed to collect a sample

History of the following:	Completed CPC Study	MEC Study					
		Participant *	Non-Participant *	p value	Collected Sample	No Sample	p value
	N=1561 n (%)	N=256 n (%)	N=82 n (%)	exact	N=256 n (%)	N=66-83 n (%)	exact
Alcohol problems	53 (3.4)	13 (6.2)	6 (7.3)	0.792	11 (4.3)	3 (4.5)	0.939
Drug problems	54 (3.5)	11 (5.2)	3 (3.7)	0.764	7 (2.8)	4 (6.1)	0.246
Unemployed when wanted to work*	161 (10.3)	26 (12.3)	9 (11.0)	0.843	**15 (5.9)**	**14 (21.2)**	**<0.001**
Depression	353 (22.7)	49 (23.2)	18 (21.9)	0.878	59 (23.1)	16 (24.2)	0.871
Suicidal thoughts/ attempt	162 (10.4)	27 (12.8)	5 (6.1)	0.143	**25 (9.8)**	**13 (19.7)**	**0.027**
Parents separated or divorced	451 (28.9)	68 (32.2)	22 (26.8)	0.369	74 (29.0)	22 (33.3)	0.495
Partner happy about pregnancy	1476 (96.4)	201 (97.6)	78 (95.1)	0.281	250 (98.8)	61 (96.8)	0.258

*Only considering women who were the part of the main CPC cohort.

4.1.2 Biomarker results

An overview of biomarker results is presented in Table 4.3. Between 15.3% and 21.5% of samples were positive for presence of FAEE depending on cut-off, with oleic and linoleic the predominant FAEE species. 16/238 (6.7%) samples were positive for opiates (morphine or codeine given antenatally) and only one sample (0.4%) tested positive for a drug of abuse, marijuana. The concentration of FAEE above the LOD ranged between 24 ng/g and 252,864 ng/g with 2 of the samples with a concentration of FAEE ≥ 100,000 ng/g.

Histograms of total FAEEs for samples with any FAEEs above the LOD (Figures 4.2 to 4.4) demonstrated a skewed distribution with several outlying values. A logarithm transformation of total FAEE for samples with any FAEEs above the LOD resulted in an approximately normal distribution (Figure 4.5).

4.1.3 Demographic Characteristics

The characteristics of women by FAEE group are summarized in Table 4.4. There was no evidence of association between FAEE concentration at several cut-offs and maternal demographic characteristics. Only cut-offs of 500 ng/g and 10,000 ng/g are presented as there was no difference seen using cut-offs of any FAEEs above the LOD, 50 ng/g, any oleic or any linoleic acid. Subjects were categorized by FAEE concentration with all subjects with FAEE ≥ 10,000 ng/g compared to all subjects with FAEE < 10,000 ng/g. The same is true for comparisons of all subjects with FAEE ≥ 500 ng/g compared to all subjects with FAEE < 500 ng/g. Women with family incomes ≥ $90,000/year were more likely to have FAEE ≥ 500 ng/g. The women in this study had the following

characteristics had a mean age of 31.4 years, were married (95%), Caucasian and well educated with 85% with at least some post-secondary education.

Table 4.3. Fatty acid ethyl ester (FAEE) and drug metabolite results (n=238) in meconium for participants of the Meconium Screening Study

Characteristic	**# Positives N=238, n**		**%**		
Drug Metabolites					
Amphetamines	0		0		
Cocaine	0		0		
Codeine	3		1.2		
Morphine	16		6.6		
Phencyclidine	0		0		
Cannabis	1		0.4		
FAEE Results					
FAEE above limit of detection	52		21.5		
FAEE ≥ 500ng/g	37		15.3		
FAEE ≥ 50 ng/g	51		21.1		
Any oleic acid	48		19.8		
Any linoleic acid	39		16.1		
Breakdown of FAEE*	**Geometric Mean** ng/g**	**Median† ng/g**	**Range ng/g**	**LOD ng/g**	**LOQ ng/g**
Total FAEE	1667.0	1331	24 – 252,864		
Palmitic	300.6	134	0 – 11,589	61	138
Palmitoleic	185.9	0	0 – 1,061	45	114
Stearic	162.7	0	0 – 9,289	37	87
Oleic	1017.7	537	0 – 144,718	40	101
Linoleic	748.5	270	0 – 77,521	43	114
Linolenic	173.4	0	0 – 6,915	16	43
Arachidonic	165.0	67	0 – 1,771	26	73

*Among samples positive for any FAEE.
**Geometric mean is a back transformation of the mean of the $\log_{10}$ transformation.
†Median is of untransformed value.

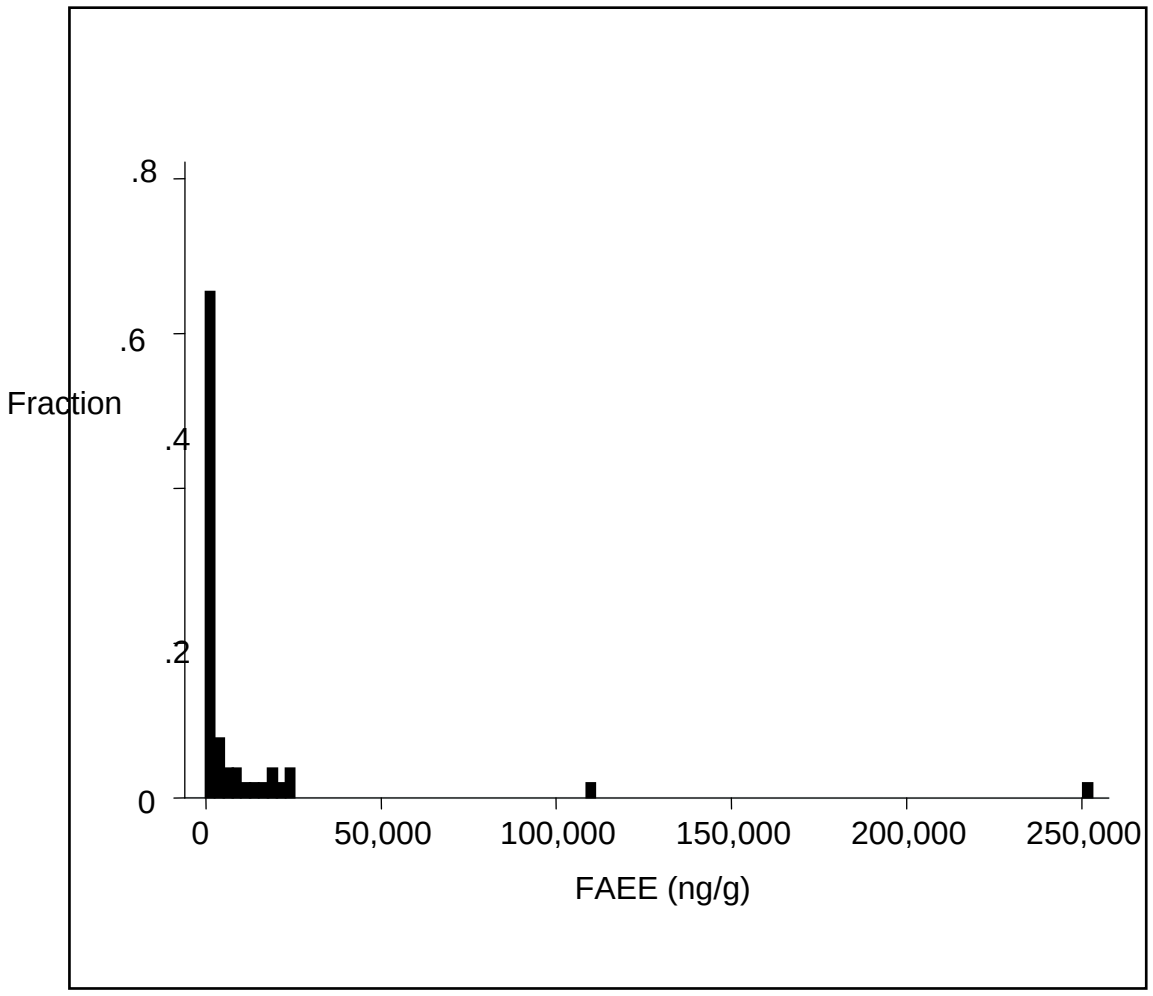


Figure 4.2. Histogram of total FAEE concentration (ng/g) in meconium for samples with any FAEEs above the limit of detection (n=52) for participants of the Meconium Screening Study

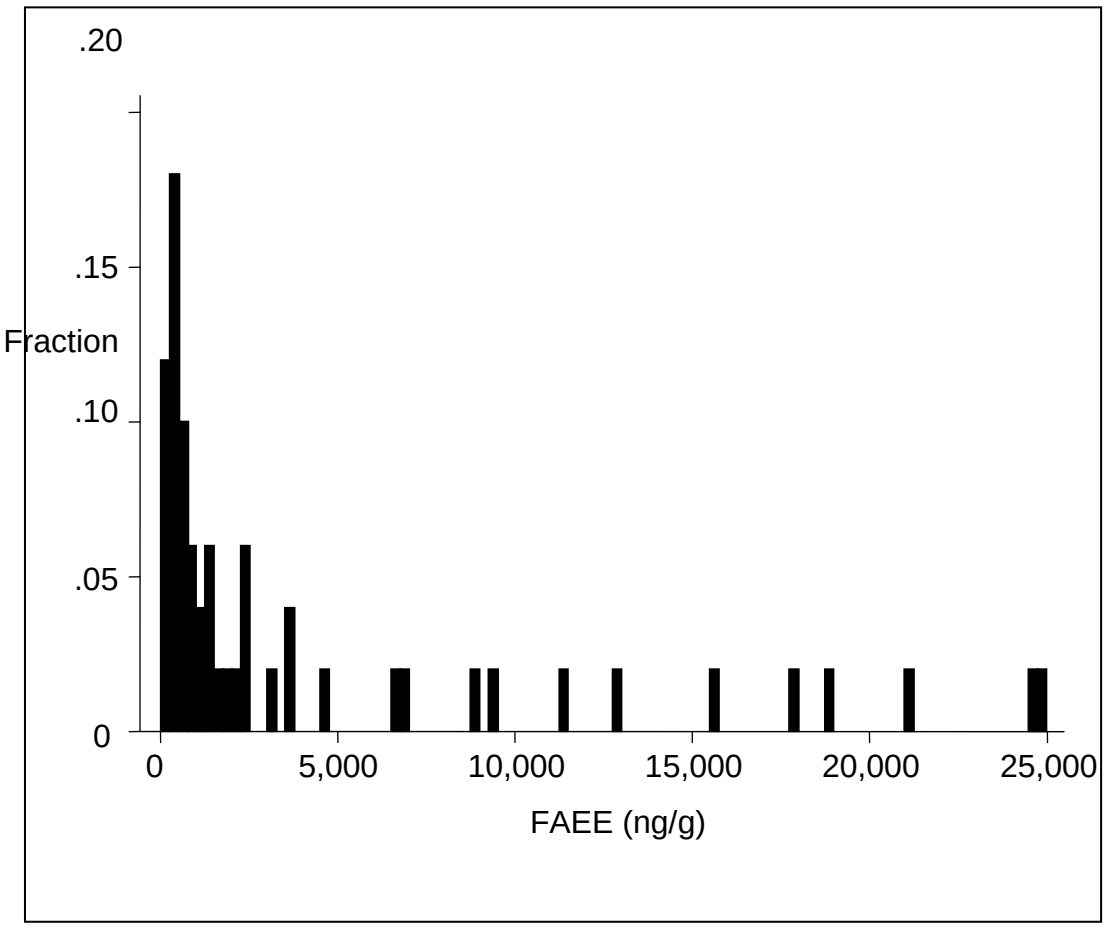


Figure 4.3. Histogram of FAEE concentration (ng/g) in meconium for samples with FAEE above the limit of detection (n=50) excluding 2 values ≥100,000 ng/g for participants of the Meconium Screening Study

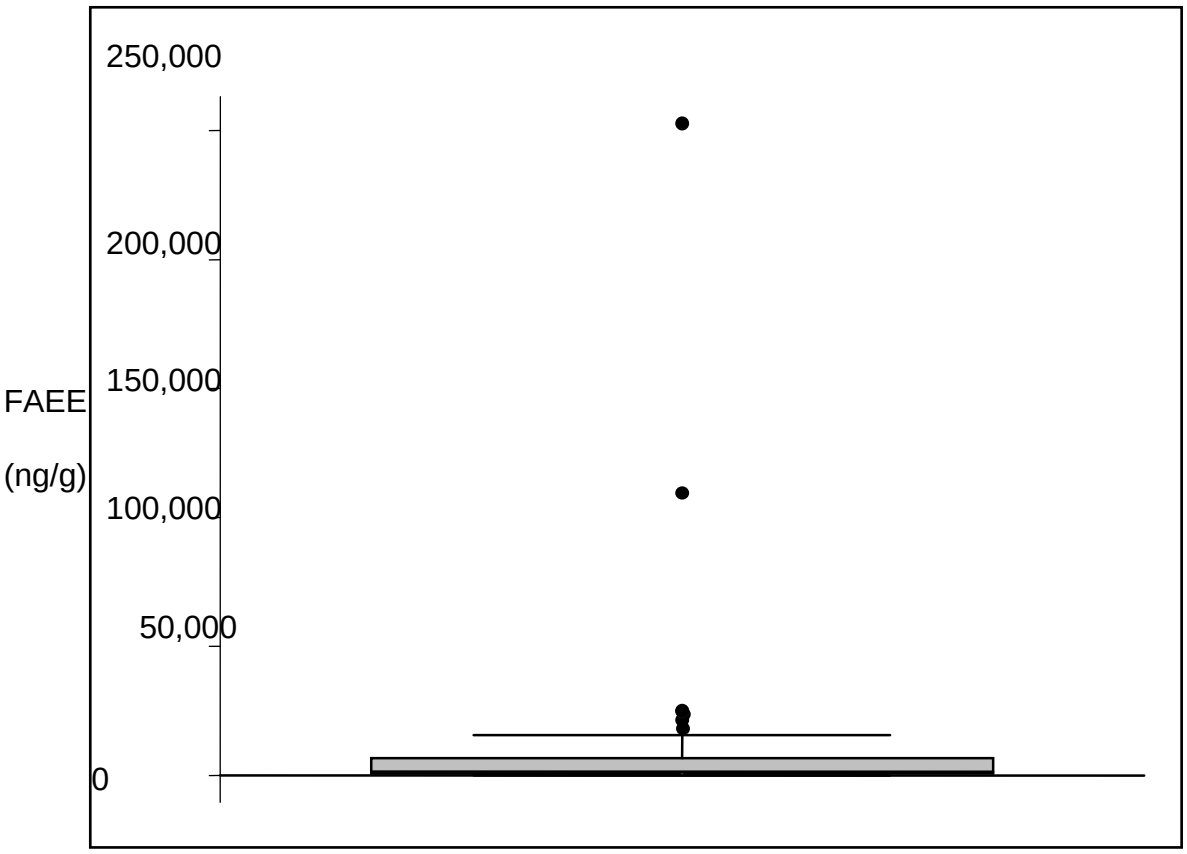


Figure 4.4. Box plot of FAEE concentration (ng/g) among FAEE concentrations above the limit of detection (n=52) for participants of the Meconium Screening Study

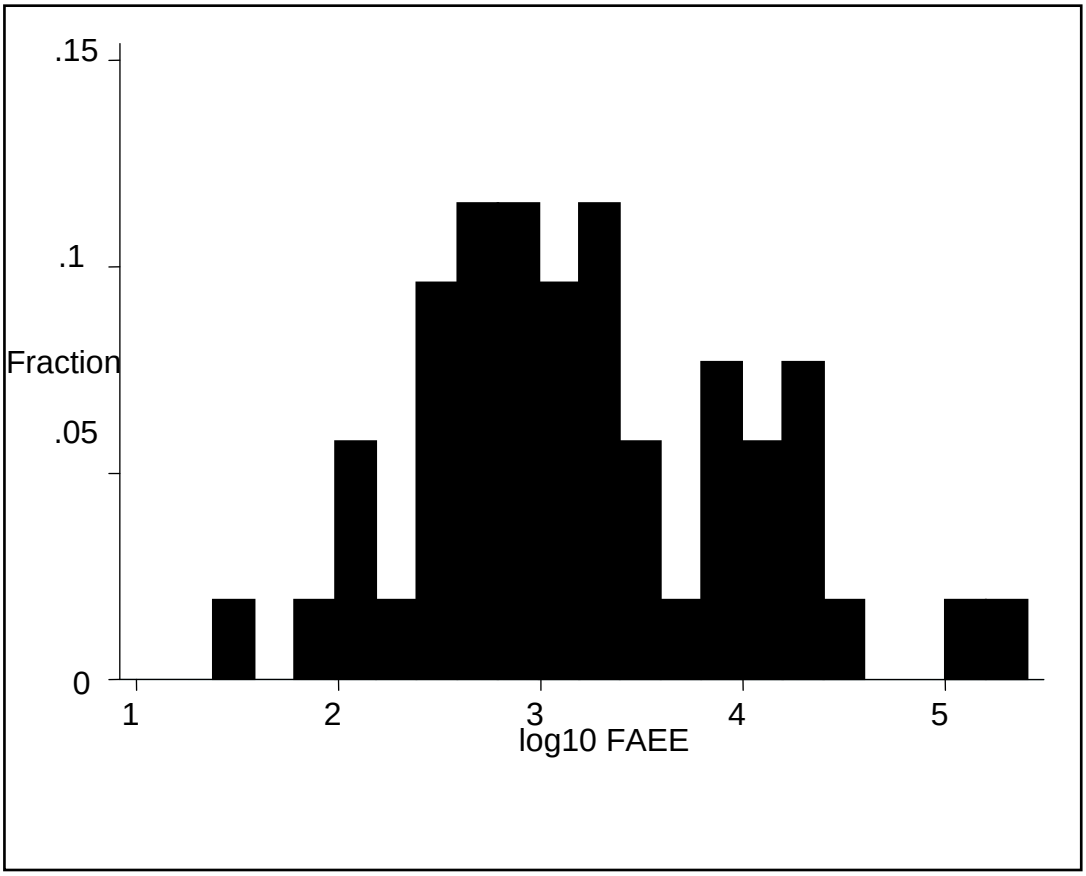


Figure 4.5. Histogram of log_{10} transformation of FAEE (ng/g) for samples that had FAEE concentrations above the limit of detection

Table 4.4. Demographic characteristics of women in the MEC Study dichotomized by FAEE concentration ≥ 10,000 ng/g or ≥ 500 ng/g

Characteristic	All Subjects	FAEE ≥10,000 ng/g*			FAEE ≥500 ng/g*		
	N=238 n (%)	+ve N=10 n (%)	-ve N=228 n (%)	p value exact	+ve N=37 n (%)	-ve N=201 n (%)	p value exact
Maternal age (yr)	31.4 sd(4.6)	32.6 sd (4.2)	31.3 sd (4.6)	0.383	32.3 sd (4.6)	31.2 sd (4.6)	0.190
Maternal age							
<25	21 (8.3)	0 (0.0)	20 (8.6)		2 (5.4)	19 (9.3)	
25-35	166 (69.0)	7 (70.0)	160 (69.0)	0.761	23 (62.2)	143 (69.8)	0.270
35+	55 (22.7)	3 (30.0)	52 (22.4)		12 (32.4)	43 (21.0)	
Previously pregnant	157 (64.9)	5 (50.0)	152 (65.5)	0.328	22 (59.5)	135 (65.9)	0.460
Previous live birth	121 (50.0)	4 (40.0)	117 (50.4)	0.749	18 (48.6)	103 (50.2)	0.858
Currently married	231 (95.9)	10 (100.0)	221 (95.7)	1.000	35 (94.6)	196 (96.1)	0.654
Caucasian	212 (88.0)	10 (100.0)	202 (87.5)	0.614	33 (89.2)	179 (87.8)	0.804
Education							
<High school	8 (3.3)	0 (0.0)	8 (3.5)	0.534	0 (0.0)	8 (3.9)	0.768
High school	28 (11.6)	2 (20.0)	26 (11.3)		4 (10.8)	24 (11.8)	
Post-secondary	205 (85.1)	8 (80.0)	197 (85.3)		33 (89.2)	172 (84.3)	
Homemaker	60 (24.9)	2 (20.0)	58 (25.1)	1.000	11 (29.7)	49 (24.0)	0.535
Household income							
≥ $90,000	116 (50.2)	5 (50.0)	111 (50.2)	1.000	**23 (67.6)**	**93 (47.2)**	**0.040**
Home owner	185 (76.8)	9 (90.0)	176 (76.2)	0.461	6 (16.2)	50 (24.5)	0.271
Current exercise							
<1 time/wk	88 (36.5)	6(60.0)	82 (35.5)	0.283	15 (40.5)	73 (35.8)	0.812
1-2.9 times/wk	114 (47.3)	3 (30.0)	111 (48.1)		16 (43.2)	98 (48.0)	
≥3 times/wk	39 (16.2)	1 (10.0)	38 (16.5)		6 (16.2)	33 (16.2)	
BMI (pre-pregnancy)							
< 20	40 (16.8)	1 (10.0)	30 (17.1)	0.285	7 (18.9)	33 (16.4)	0.942
20-29.9	112 (47.1)	3 (30.0)	109 (47.8)		17(46.0)	95 (47.3)	
≥ 30	86 (36.1)	6 (60.0)	80 (35.1)		13 (35.1)	73 (36.3)	

*Subjects were categorized by FAEE concentration with all subjects with FAEE ≥ 10,000 ng/g compared to all subjects with FAEE < 10,000 ng/g and all subjects with FAEE ≥ 500 ng/g compared to all subjects with FAEE < 500 ng/g.

4.1.4 Lifestyle Characteristics

Of note, 80% of women reported any alcohol use in the year prior to pregnancy and 30% reported binge episodes (Figures 4.6 to 4.8). In general, women reported that they stopped drinking alcohol once they were aware they were pregnant. Overall frequency of alcohol use, amount consumed per occasion and number of binge episodes decreased with pregnancy.

There was no evidence of association between alcohol use prior to pregnancy, binge drinking pattern, self-reported alcohol use during pregnancy, and drinking pattern and positive for FAEEs at a cut off of 500 ng/g and 10,000 ng/g (Tables 4.5 to 4.7). There was no evidence of association between alcohol use in prior pregnancies, personal and family history of alcohol use and T-ACE scores and positive for FAEEs at a cut off of 500 ng/g and 10,000 ng/g. Women whose infants had a high concentration of FAEE (≥10,000 ng/g) did not have a positive T-ACE (Figure 4.8). There was no evidence of association between the derived values of average amount (oz) of absolute alcohol consumed per day, absolute alcohol consumed per week, and average amount (oz) of absolute alcohol consumed per actual drinking days and meconium FAEEs (data not shown). There was no evidence of association between maternal self-report when concentration of FAEE was examined as individual, total or selected FAEEs; 83% of women who reported weekly alcohol use in the third trimester had infants with samples negative for FAEEs. No women reported more than one drink per occasion in the third trimester. There was no evidence of difference between the characteristics of women whose infants had FAEE concentrations ≥10,000ng/g and women whose infants had lower FAEE concentrations and 88% of mothers whose infants had meconium samples

positive for FAEE sat a cut-off of 10,000 ng/g denied alcohol use in the third trimester. Logistic regression modeling was not performed as there were too few variables on bivariate analysis that were significant.

In general, women decreased or stopped smoking cigarettes and using street drugs during pregnancy with 22% smoking prior to pregnancy and 12% smoking in the third trimester while 9% used street drugs (predominantly cannabis) prior to pregnancy with only 3.8% using during pregnancy.

In this study, there was no evidence of association between smoking at any time, drug use, food habits, diet and vitamin use and meconium positive for FAEEs at a cut off of 500 ng/g and 10,000 ng/g. Dairy was more likely to always be included in the diet of women with infants who had high concentrations of FAEE. There was no evidence of difference in intake of meat, soy, caffeine, herbal teas, soda pop, bottled water, grain products, fruit, junk food or self-reported vegan status.

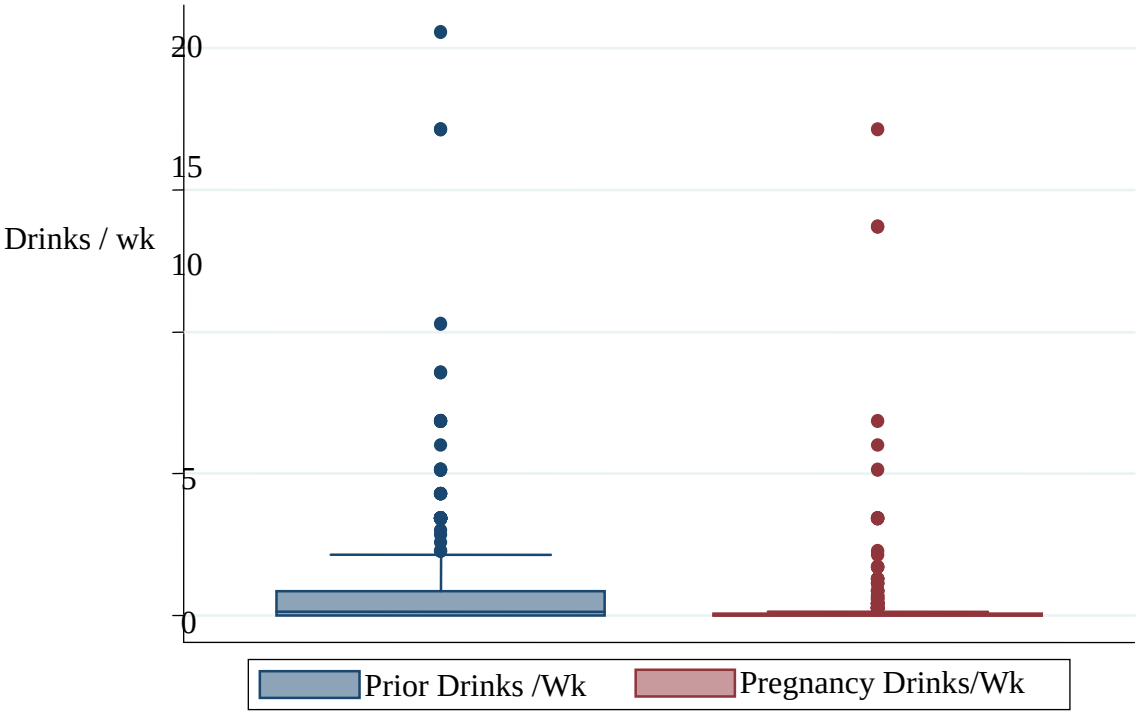


Figure 4.6. Box plot of drinks per week prior to and during pregnancy based on self-reported frequency of subjects in the Meconium Screening Study

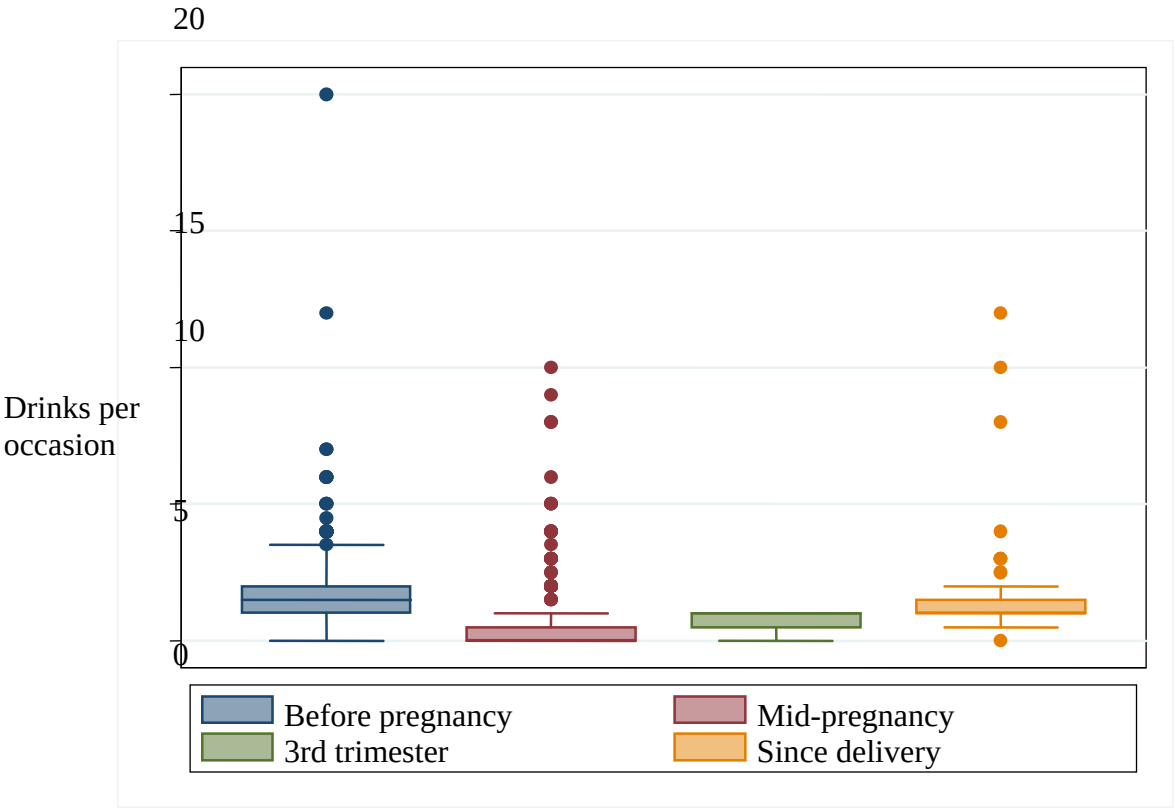


Figure 4.7. Box plot of drinks per occasion prior to pregnancy, mid-pregnancy, in the third trimester and following delivery based on self-reported frequency of alcohol use of subjects in the Meconium Screening Study

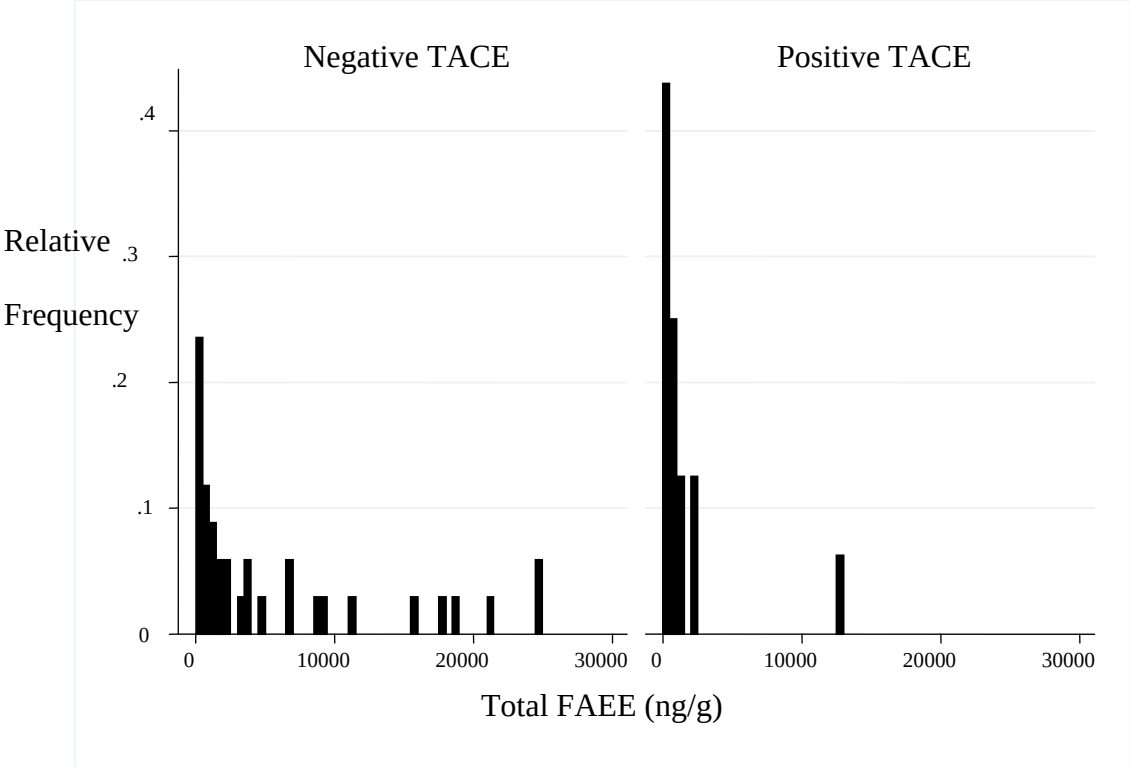


Figure 4.8. Histogram of relative frequency of FAEE concentration in meconium by T-ACE score for samples with any FAEE concentration above the limit of detection (2 concentrations greater than 100,000 ng/g were excluded from the negative T-ACE group in this figure)

Table 4.5. Alcohol use prior to and during pregnancy of women in the MEC Study dichotomized by FAEE concentration ≥ 10,000 ng/g or ≥ 500 ng/g

Characteristic	FAEE ≥10,000 ng/g*			FAEE ≥500 ng/g*		
	+ve N=10 n (%)	-ve N=228 n (%)	p value exact	+ve N=37 n (%)	-ve N=201 n (%)	p value exact
Binge episodes in 12 mo. prior to pregnancy						
Yes	3 (30.0)	52 (26.3)	0.589	11 (29.7)	54 (26.6)	0.691
Any alcohol in 12 mo. prior to pregnancy						
Yes	9 (90.0)	180 (77.9)	0.694	29 (78.4)	161 (77.4)	0.304
Drinks per Week Prior to Pregnancy						
No Alcohol	2 (20.0)	53 (22.8)		10 (27.0)	45 (22.0)	
<1 Drink/week	6 (60.0)	120 (51.7)	1.000	21 (56.8)	105 (51.2)	0.504
1-4.9 Drinks/week	2 (20.0)	54 (23.3)		6 (16.2)	50 (24.4)	
≥ 5 Drinks/week	0 (0.0)	5 (2.2)		0 (0.0)	5 (2.4)	
Alcohol prior to pregnancy						
>1 drink/week	2 (20.0)	59 (25.4)	1.000	6 (16.2)	55 (26.8)	0.218
Any alcohol during 1st trimester, including prior to pregnancy recognition						
Yes	3 (30.0)	72 (31.0)	1.000	11 (29.7)	71 (34.0)	0.614
Drinks per Week During Pregnancy						
No Alcohol	7 (70.0)	160 (69.0)		27 (73.0)	140 (68.3)	
<1 Drink/week	3 (30.0)	59 (25.4)	1.000	9 (24.3)	53 (25.9)	0.963
1-4.9 Drinks/week	0 (0.0)	11 (4.7)		1 (2.7)	10 (4.9)	
≥ 5 Drinks/week	0 (0.0)	2 (0.9)		0 (0.0)	2 (1.0)	
Binge Episodes During Pregnancy						
>1	0 (0.0)	9 (4.7)	1.000	0 (0.0)	9 (4.4)	1.000
Partner Alcohol Freq						
No Alcohol	2 (20.0)	48 (20.7)		8 (21.6)	42 (20.5)	
Monthly	2 (20.0)	57 (24.6)		10 (27.0)	49 (23.9)	
Weekly	3(30.0)	76 (32.8)	0.554	9 (24.3)	70 (34.1)	0.769
Several times/week	3 (30.0)	28 (12.1)		6 (16.2)	25 (12.2)	
Daily	0 (0.0)	23 (9.9)		4 (10.8)	19 (9.3)	

*Subjects were categorized by FAEE concentration with all subjects with FAEE ≥ 10,000 ng/g compared to all subjects with FAEE < 10,000 ng/g and all subjects with FAEE ≥ 500 ng/g compared to all subjects with FAEE < 500 ng/g.

Table 4.6. T-ACE scores and history of alcohol problems or use of women in the MEC Study dichotomized by FAEE concentration ≥ 10,000 ng/g or ≥ 500 ng/g

Characteristic	FAEE ≥10,000 ng/g*			FAEE ≥ 500 ng/g*		
	+ve N=10 n (%)	-ve N=228 n (%)	p value exact	+ve N=37 n (%)	-ve N=201 n (%)	p value exact
T-ACE ≥2						
Yes	**1 (11.1)**	**87 (38.1)**	**0.039**	9 (24.3)	79 (38.5)	0.098
T-ACE ≥3						
Yes	0 (0.0)	17 (9.4)	1.000	2 (5.4)	15 (7.3)	0.675
Any +ve non-tolerance T-ACE criteria						
Yes	0 (0.0)	25 (10.8)	0.605	4 (18)	21 (10.2)	0.917
Family History of Alcohol Problems						
Yes	2 (20.0)	72 (31.2)	0.728	7 (18.9)	66 (32.3)	0.102
History of Alcohol problems						
Yes	0 (0.0)	10 (4.4)	1.000	0 (0.0)	10 (4.9)	0.368
Alcohol use in previous pregnancy						
Yes	2 (20.0)	34 (14.7)	0.647	7 (18.9)	30 (14.6)	0.466

*Subjects were categorized by FAEE concentration with all subjects with FAEE ≥ 10,000 ng/g compared to all subjects with FAEE < 10,000 ng/g and all subjects with FAEE ≥ 500 ng/g compared to all subjects with FAEE < 500 ng/g.

Table 4.7. Diet and food habits of women in the MEC Study dichotomized by FAEE concentration ≥ 10,000 ng/g or ≥ 500 ng/g

Characteristic	FAEE ≥10,000 ng/g*			FAEE ≥ 500 ng/g*		
	+ve N=10 n (%)	-ve N=228 n (%)	p value exact	+ve N=37 n (%)	-ve N=201 n (%)	p value exact
Prenatal vitamins						
No	0 (0.0)	8 (3.6)	1.000	1 (3.0)	8 (3.6)	0.876
Run out of food						
Yes	0 (0.0)	8 (3.5)	1.000	0 (0.0)	8 (3.9)	0.610
Skip breakfast						
Often	0 (0.0)	44 (19.1)	0.215	4 (10.8)	40 (19.6)	0.252
Skip lunch						
Often	0 (0.0)	7 (3.2)	0.818	1 (2.7)	6 (3.0)	1.000
Skip dinner						
Often	0 (0.0)	3 (1.3)	0.477	1 (2.7)	2 (1.0)	0.109
Vegetable intake						
Always	9 (90.0)	167 (72.3)	0.295	31 (83.8)	191 (93.6)	0.088
Dairy Intake						
Always	**10 (100.0)**	**148 (64.1)**	**0.043**	18 (48.7)	133 (65.2)	0.065
Weight prior to pregnancy			0.758			0.775
Lower	1 (10.0)	15 (6.5)		3 (8.1)	13 (6.4)	
About same	6 (60.0)	133 (57.6)		20 (54.1)	119 (58.3)	
Higher	3 (30.0)	83 (35.9)		14 (37.8)	72 (35.3)	

*Subjects were categorized by FAEE concentration with all subjects with FAEE ≥ 10,000 ng/g compared to all subjects with FAEE < 10,000 ng/g and all subjects with FAEE ≥ 500 ng/g compared to all subjects with FAEE < 500 ng/g.

4.1.5 History of Life Events and Psychosocial Characteristics

There was no evidence of association between history of emotional, physical, sexual, and financial abuse or neglect and positive meconium samples. There was no evidence of difference between the psychosocial characteristics of women with children with positive samples versus those with negative samples (Table 4.8). Of note, 33.5% of women in the study reported a history of abuse; and 10% of women reported a history of suicidal thoughts or attempts (Table 4.9).

Table 4.8. History of life events and abuse of women in the MEC Study dichotomized by FAEE concentration ≥ 10,000 ng/g or ≥ 500 ng/g

Characteristic	All Subjects	FAEE ≥10,000 ng/g*			FAEE ≥500 ng/g*		
	N=238 n (%)	+ve N=10 n (%)	-ve N=228 n (%)	p value exact	+ve N=37 n (%)	-ve N=201 n (%)	p value exact
Emotional Abuse							
Yes	59 (24.4)	2 (20.0)	57 (24.6)	1.000	9 (24.3)	50 (24.4)	0.993
Physical Abuse							
Yes	32 (13.2)	1 (10.0)	31 (13.4)	1.000	6 (16.2)	26 (12.7)	0.598
Sexual Abuse							
Yes	35 (14.5)	1 (10.0)	34 (14.7)	1.000	5 (13.5)	30 (14.6)	0.858
Financial Abuse							
Yes	10 (4.1)	0 (0.0)	10 (4.3)	1.000	0 (0.0)	10 (4.9)	0.368
Neglected							
Yes	6 (2.5)	0 (0.0)	6 (2.6)	1.000	2 (5.4)	4 (1.9)	0.229
Any Abuse							
Yes	81 (33.5)	2 (20.0)	79 (34.1)	0.503	12 (32.4)	69 (3.7)	0.884
Unemployed when wanted to work							
Yes	15 (6.2)	1 (10.0)	14 (6.1)	0.481	1 (2.7)	14 (6.9)	0.479
Depression							
Yes	56 (23.2)	1 (10.0)	55 (23.8)	0.461	10 (27.0)	46 (22.6)	0.553
Suicidal thoughts or attempt							
Yes	25 (10.4)	0 (0.0)	25 (10.8)	0.605	5 (13.5)	20 (9.8)	0.556
Parents separated or divorced							
Yes	74 (30.8)	3 (30.0)	71 (30.9)	0.925	11 (29.7)	63 (31.0)	0.874

*Subjects were categorized by FAEE concentration with all subjects with FAEE ≥ 10,000 ng/g compared to all subjects with FAEE < 10,000 ng/g and all subjects with FAEE ≥ 500 ng/g compared to all subjects with FAEE < 500 ng/g.

Table 4.9. Drug and cigarette use of women in the MEC Study dichotomized by FAEE concentration ≥ 10,000 ng/g or ≥ 500 ng/g

Characteristic	FAEE ≥10,000 ng/g*			FAEE ≥500 ng/g*		
	+ve N=10 n (%)	-ve N=228 n (%)	p value exact	+ve N=37 n (%)	-ve N=201 n (%)	p value exact
Any smoking in 12 months prior to pregnancy Yes	3 (30.0)	42 (18.1)	0.400	5 (13.5)	41 (19.6)	0.495
Any smoking during pregnancy Yes	1 (10.0)	31 (13.)	1.000	3 (8.1)	30 (14.3)	0.942
Any street drugs in 12 months prior to pregnancy Yes	1 (10.0)	17 (7.4)	0.547	1 (2.7)	18 (8.7)	0.323
Any street drugs during first trimester Yes	0 (0.0)	7 (3.0)	1.000	0 (0.0)	8 (3.9)	0.611
Drug problems in past Yes	0 (0.0)	7 (3.0)	1.000	0 (0.0)	7 (3.4)	0.599

*Subjects were categorized by FAEE concentration with all subjects with FAEE ≥ 10,000 ng/g compared to all subjects with FAEE < 10,000 ng/g and all subjects with FAEE ≥ 500 ng/g compared to all subjects with FAEE < 500 ng/g.

4.1.6 Birth Outcomes

There were differences for birth outcomes by meconium positive for FAEEs at a cut off of 500 ng/g and 10,000 ng/g (Table 4.10). Male infants were more likely to have meconium samples positive for FAEE. Male infants make up 49% of the sample but represent 66.7% of the positive samples at a cut off of 500 ng/g. Of note, 28.6% of the infants with a FAEE in meconium concentration above 10,000 ng/g had Apgar scores <7 at 1 minute compared to 12% in the group with FAEEs in meconium below 10,000 ng/g. This was not statistically significant given small cell size in the positive group and only represents 2 infants. 91.7% of the positive samples at a cut off of 500 ng/g were collected at Foothills Medical Centre versus 71.7% of the negative samples.

Table 4.10. Birth outcomes, pregnancy complications and postnatal events of women in the MEC Study dichotomized by FAEE concentration ≥ 10,000 ng/g or ≥ 500 ng/g

Characteristic	FAEE ≥10,000 ng/g*			FAEE ≥500 ng/g*		
	+ve N=10 n (%)	-ve N=228 n (%)	p value exact	+ve N=37 n (%)	-ve N=201 n (%)	p value exact
Birth weight (g)	3523.1 sd(511.7)	3466.0 sd(452.1)	0.727	3473.6 sd(454.9)	34673 sd(453.8)	0.995
Birth length (cm)	52.3 sd(2.1)	52.0 sd(2.3)	0.448	52.2 sd(2.1)	52.0 sd(2.3)	0.673
Birth Hospital FMC	9 (90.0)	173 (74.6)	0.458	**33 (91.7)**	**147 (71.7)**	**0.012**
Male infant	4 (50.0)	107 (48.2)	1.000	**22 (64.7)**	**90 (45.0)**	**0.033**
Preterm delivery (37 weeks) Preterm	1 (12.5)	5 (2.7)	0.195	2 (6.1)	4 (2.1)	0.210
Vaginal delivery	5 (62.5)	173 (77.9)	0.306	29 (85.3)	149 (76.0)	0.483
Gestational Diabetes/ Hyperglycemia** Positive	0 (0.0)	4 (1.7)	1.0002	0 (0.0)	4 (1.9)	0.302
Apgar scores at 1 minute <7	2 (28.6)	23 (12.1)	0.218	4 (16.0)	21 (12.2)	0.532

*Subjects were categorized by FAEE concentration with all subjects with FAEE ≥ 10,000 ng/g compared to all subjects with FAEE < 10,000 ng/g and all subjects with FAEE ≥ 500 ng/g compared to all subjects with FAEE < 500 ng/g.

**Subjects from Low Risk Maternity Clinic. Women with Gestational Diabetes would likely have been transferred to the care of an Obstetrician.

4.1.7 T-ACE and Lifestyle Characteristics

The T-ACE identified women with risky patterns of alcohol and drug use (Table 4.11). Using a cut-off of 2 on the T-ACE score, 88/238 (37.0%) of subjects had a positive T-ACE score (at risk for alcohol use during pregnancy). Women with a positive T-ACE were more likely to report: alcohol use in a previous pregnancy, binge episodes prior to and during pregnancy, any alcohol use prior to and during pregnancy, and any street drug use in the 12 months prior to pregnancy. Women with a positive T-ACE were more likely to report a history of being sexually abused, and a history of any abuse (Table 4.12).

Table 4.11. Alcohol use prior to and during pregnancy of women in the MEC Study by T-ACE score

Characteristic	T-ACE*		
	+ve N=88 n (%)	-ve N=150 n (%)	p value exact
Binge episodes in 12 mo. prior to pregnancy			
Yes	**36 (40.9)**	**29 (18.8)**	**0.006**
Any alcohol in 12 mo. prior to pregnancy			
Yes	**87 (98.9)**	**102 (66.7)**	**<0.001**
Drinks per Week Prior to Pregnancy			
No Alcohol	**1 (1.1)**	**54 (35.1)**	**<0.001**
<1 Drink/week	**43 (48.9)**	**83 (53.9)**	
1-4.9 Drinks/week	**40 (45.5)**	**16 (10.4)**	
≥ 5 Drinks/week	**4 (4.5)**	**1 (0.7)**	
Alcohol prior to pregnancy			
>1 drink/week	**44 (50.0)**	**17 (11.0)**	**<0.001**
Any alcohol during 1st trimester, including prior to pregnancy recognition			
Yes	**58 (65.9)**	**17 (11.0)**	**<0.001**
Drinks per Week During Pregnancy			
No Alcohol	**30 (34.1)**	**137 (89.0)**	**<0.001**
<1 Drink/week	**46 (52.3)**	**16 (10.4)**	
1-4.9 Drinks/week	**10 (11.4)**	**1 (0.6)**	
≥ 5 Drinks/week	**2 (2.3)**	**0 (0.0)**	
Binge Episodes During Pregnancy			
>1 Episode of 5 or more drinks	**6 (6.8)**	**3 (1.9)**	**0.012**
Partner Alcohol Freq			
No Alcohol	**5 (5.7)**	**45 (29.2)**	**<0.001**
Monthly	**22 (25.0)**	**37 (24.0)**	
Weekly	**35 (39.8)**	**44 (28.6)**	
Several times/week	**13 (14.8)**	**18 (11.7)**	
Daily	**13 (14.8)**	**10 (6.5)**	

*T-ACE score ≥ 2 is positive.

Table 4.12. History of life events and abuse of women in the MEC Study by T-ACE score

Characteristic	All Subjects	T-ACE*		
History of the following:	**N=238 n (%)**	**+ve N=88 n (%)**	**-ve N=150 n (%)**	**p value exact**
Emotional Abuse				
Yes	59 (24.4)	24 (27.3)	35 (22.7)	0.440
Physical Abuse				
Yes	32 (13.2)	16 (18.2)	16 (10.4)	0.114
Sexual Abuse				
Yes	35 (14.5)	**19 (21.6)**	**16 (10.4)**	**0.022**
Financial Abuse				0.176
Yes	10 (4.1)	6 (6.8)	4 (2.6)	
Neglected				0.194
Yes	6 (2.5)	4 (4.6)	2 (1.3)	
Any Abuse				
Yes	81 (33.5)	**39 (44.3)**	**42 (27.3)**	**0.011**
Unemployed when wanted to work				
Yes	15 (6.2)	7 (8.0)	8 (5.2)	0.417
Depression				
Yes	56 (23.2)	21 (23.9)	35 (22.9)	0.875
Suicidal thoughts or attempt				
Yes	25 (10.4)	13 (14.8)	12 (7.8)	0.123
Parents separated or divorced				
Yes	74 (30.8)	32 (36.8)	42 (27.5)	0.147
Low Parental Expectancy**				
Yes	24.8	**29 (35.8)**	**30 (22.4)**	**0.040**

*T-ACE score ≥ 2 is positive.

**Low Postpartum Parenting Expectancy Survey as defined by lowest 25%ile of scores.

4.2 Concentration of FAEE in Meconium and Child Development

4.2.1 Recruitment and Participation

A flowchart of recruitment participation and loss to follow up is presented in Figure 4.9. In total, 196 subjects from the Meconium Screening Study were eligible to participate in the follow up study as of May 2007. Of those approached, 156 women (80.0%) agreed to participate with (93.6%) of those agreeing to participate completing follow up visits or standardized questionnaires. Ten subjects were lost to follow up or changed their mind about participating after initially consenting resulting in an overall participation rate of 73%. Of those participating, 132 subjects had completed full follow up or provided the parent report portion of the follow up by May 2007. Analyses are based on these 132 subjects.

Compared to women who participated in the study, women who did not participate or were lost to follow up were more likely to be of non-Caucasian ethnicity, have a lower degree of education, a lower household income, were more likely to report daily smoking, exercise less frequently, report a family history of alcohol problems, and report a history of suicide attempts (Tables 4.13 and 4.14). This is consistent with a more marginalized group that is less likely to remain engaged with research. There was no evidence of difference in participation by FAEE status; however, there was a tendency towards a higher proportion of meconium positive for FAEEs in the participant group.

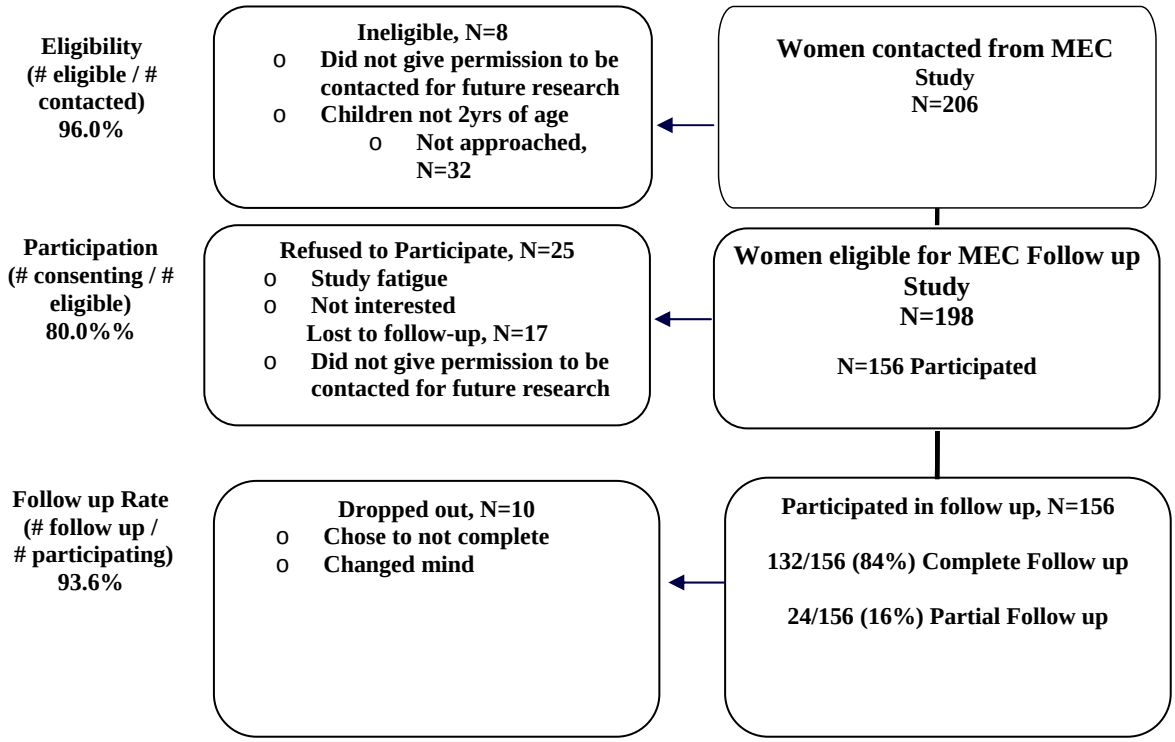


Figure 4.9. Study flowchart of recruitment of women participating or approached to participate in the Meconium Follow Up Study

Table 4.13. Sociodemographic and lifestyle characteristics of women who participated in the MEC Follow Up Study compared to women who did not participate or were lost to follow up

Characteristic	MEC Follow Up Study		
	Participant	**Non-Participant**	**p value**
	N=156 n (%)	**N=50 n (%)**	
Maternal age (yrs)	31.08 sd 4.6	29.9 sd 5.3	0.147
Maternal age			0.537
<25	11 (7.05)	6 (12.0)	
25-35	111 (71.1)	33 (66.0)	
35+	34 (21.8)	11 (22.0)	
Not married	6 (3.9)	4 (8.0)	0.262
Non-Caucasian	**16 (10.3)**	**13 (26.0)**	**0.009**
Education			**0.002**
< High school	**4 (2.6)**	**5 (10.0)**	
High school	**15 (9.7)**	**12 (24.0)**	
Post-secondary	**136 (87.7)**	**33 (66.0)**	
Household Income per year			0.079
<$40,000	18 (12.2)	10 (20.4)	
$40,000 – $79,999	52 (35.4)	22 (44.9)	
>$80,000	77 (52.4)	17 (34.7)	
Any food bank use*	4 (2.58)	1 (2.0)	1.000
Homemaker as primary occupation*	37 (23.9)	12 (24.0)	0.985
Daily Smoking*	**17 (10.9)**	**16 (32.0)**	**0.003**
T-ACE +ve	55 (35.6)	14 (28.0)	0.344
Alcohol*			0.217
< 1 time/month	42 (84)	114 (73.1)	
Several times/month	8 (16.0)	36 (23.1)	
Daily	0 (0.0)	6 (3.8)	
Any Drug Use*	14 (9.0)	4 (8.0)	0.823
Exercise			0.055
≥3 times/wk	21 (13.6)	10 (20.0)	
1-2.9 times/wk	83 (53.6)	17 (34.0)	
<1 time/wk	51 (32.9)	23 (46.0)	

*Within 12 months prior to pregnancy

Table 4.14. History of life events and birth characteristics of women who participated in the MEC Follow up study compared to women who did not participate or were lost to follow up

Characteristic	MEC Follow Up Study		
	Participant	**Non-Participant**	**p value**
	N=156 n (%)	**N=50 n (%)**	**exact**
Family history of alcohol problems	**38 (24.5)**	**20 (40.0)**	**0.046**
Personal history of alcohol problems	7 (4.5)	3 (6.0)	0.709
Personal history of drug problems	4 (2.6)	3 (6.0)	0.365
Unemployed when wanted to work*	29 (18.8)	13 (26.5)	0.247
Depression	29 (18.7)	15 (30.0)	0.113
Suicidal thoughts/ attempt	**18 (11.7)**	**12 (24.0)**	**0.040**
History of any abuse	43 (27.6)	16 (32.0)	0.591
Parents separated or divorced	42 (27.1)	20 (40.8)	0.077
Partner happy about pregnancy	152 (98.7)	49 (100.0)	0.423
FAEE ≥ LOD	37(24.18)	9 (18.0	0.365
FAEE ≥ 500 ng/g	27 (17.7)	4 (8.0)	0.116
FAEE ≥ 10,000 ng/g	9 (5.9)	1 (2.0)	0.456
Gave birth at FMC	115 (73.7)	32 (64.0)	0.186

4.2.2 Maternal and Child Characteristics Prior to Time of Follow up

The demographic characteristics of women by FAEE group are summarized in Table 4.15. Only cut-offs of 500 ng/g and above LOD are presented as there was no difference seen using cut-offs of any FAEE above the LOD, 500 ng/g, 5000 ng/g, 10,000 ng/g any oleic or any linoleic acid. Subjects were categorized by FAEE concentration with all subjects with FAEE ≥ LOD compared to all subjects with FAEE < LOD. The same is true for comparisons of all subjects with FAEE ≥ 500 ng/g compared to all subjects with FAEE < 500 ng/g. In addition, 500 ng/g and any FAEE greater than the LOD are consistent with the concentration used by the testing lab and in the literature for an elevated concentration of FAEE (97;98;108).

The women in this study had the following characteristics: a mean age of 33.1 years, were married (97%), Caucasian (90.8%) and well educated with 87% with at least some post-secondary education. Women with family incomes ≥ $90,000/year were more likely to have FAEE ≥ 500 ng/g but this did not reach statistical significance.

Table 4.15. Demographic characteristics of women in the MEC Follow Up Study dichotomized by FAEE concentration ≥ LOD or ≥ 500 ng/g

Characteristic	All Subjects	FAEE ≥ LOD*			FAEE ≥ 500 ng/g*		
	N=132** n (%)	+ve N=32 n (%)	-ve N=100† n (%)	p value exact	+ve N=23 n (%)	-ve N=108 n (%)	p value exact
Maternal age (yrs)‡	33.1 sd(4.6)	33.9 sd (5.1)	33.9 sd (4.5)	0.322	33.9 sd (5.4)	33.0 sd (5.5)	0.429
Maternal age							
<25	8 (6.1)	2 (6.2)	6 (6.0)		1 (4.4)	7 (6.5)	
25-35	93 (70.5)	19 (59.4)	74 (74.0)	0.232	15 (65.2)	78 (71.5)	0.725
35+	31 (23.5)	11 (34.4)	20 (20.0)		7 (30.4)	24 (22.0)	
Previously pregnant	92 (69.7)	19 (59.4)	73 (73.0)	0.185	14 (60.9)	78 (71.6)	0.326
Previous live birth	74 (56.1)	15 (46.9)	59 (59.0)	0.306	12 (52.2)	62 (56.9)	0.818
Currently married	127 (97.0)	31 (97.0)	96 (97.0)	1.000	22 (96.0)	105 (97.2)	0.543
Caucasian	119 (90.8)	27 (84.4)	92 (92.9)	0.165	19 (82.6)	100 (92.6)	0.223
Education							
<High school	4 (3.1)	0 (0.0)	4 (4.0)	0.702	0 (0.0)	4 (3.7)	0.743
High school	13 (9.9)	3 (9.4)	10 (10.1)		3 (13.0)	10 (9.3)	
Post-secondary	114 (87.0)	29 (90.6)	85 (85.9)		20 (87.0)	94 (87.0)	
Homemaker	32 (24.4)	9 (28.1)	23 (23.2)	0.638	8 (34.8)	24 (22.2)	0.283
Household income ≥ $90,000	66 (52.8)	19 (63.3)	47 (49.0)	0.185	15 (71.4)	51 (49.0)	0.061
Home owner	104 (79.4)	28 (87.5)	76 (76.7)	0.220	20 (87.0)	84 (77.8)	0.406
Current exercise							
<1 time/wk	42 (32.1)	10 (31.3)	32 (32.0)	0.811	8 (34.8)	34 (31.5)	0.947
1-2.9 times/wk	72 (55.0)	19 (59.4)	53 (53)		12 (52.2)	60 (55.6)	
≥3 times/wk	17 (13.0)	3 (9.4)	14 (14.0)		3 (13.0)	14 (13.0)	
BMI (pre-pregnancy)							
< 20	22 (16.9)	5 (15.6)	17 (17.3)	0.685	4 (17.4)	18 (16.8)	0.788
20-29.9	60 (46.1)	17 (53.1)	43 (43.9)		12(52.2)	48 (44.9)	
≥ 30	48 (36.9)	10 (31.3)	38 (38.8)		7 (30.4)	41 (38.3)	

*Subjects were categorized by FAEE concentration with all subjects with FAEE ≥ LOD compared to all subjects with FAEE < LOD and all subjects with FAEE ≥ 500 ng/g compared to all subjects with FAEE < 500 ng/g.

**N varied between 131 and 132

†N varied between 99 and 100

‡Maternal age at follow up

4.2.3 Maternal and Child Characteristics Prior to Time of Follow up

Alcohol and drug use during pregnancy of women by FAEE group are summarized in Table 4.16. There was no evidence of difference in drug and alcohol use reported during pregnancy between the FAEE groups. There was a tendency that did not reach statistical significance however for a greater proportion of subjects in the FAEE negative group to report frequent alcohol use prior to pregnancy recognition, greater than 2 drinks per sitting prior to pregnancy recognition, T-ACE positive, binge episodes prior to pregnancy recognition, alcohol use in the 3rd trimester, and 1-5 drinks per week during pregnancy.

Table 4.16. Preconception and prenatal psychosocial characteristics of women in the MEC Follow Up Study dichotomized by FAEE concentration ≥ LOD or ≥ 500 ng/g

Characteristic	All Subjects	FAEE ≥ LOD*			FAEE ≥ 500 ng/g*		
	N=132 n (%)	+ve N=32 n (%)	-ve N=100 n (%)	p value	+ve N=23 n (%)	-ve N=108 n (%)	p value
History of alcohol problems	6 (4.6)	1 (3.1)	5 (5.1)	1.000	0 (0.0)	6 (5.6)	0.590
History of drug problems	4 (3.1)	1 (3.1)	3 (3.0)	1.000	0 (0.0)	4 (3.7)	1.000
Depression	28 (21.4)	8 (25.0)	20 (20.2)	0.622	6 (26.1)	22 (20.4)	0.579
Suicidal thoughts/ attempt	17 (13.1)	3 (9.4)	14 (14.3)	0.562	2 (8.7)	15 (14.0)	0.736
History of any abuse	37 (28.0)	3 (9.4)	34 (34.0)	0.006	2 (8.7)	35 (32.1)	0.023
Smoked during pregnancy	21 (15.9)	3 (9.4)	18 (18.0)	0.163	2 (8.7)	19 (17.4)	0.059
Prior to pregnancy ≥2 drinks per sitting	44 (33.3)	7 (21.9)	37 (37.0)	0.135	5 (21.7)	39 (35.8)	0.231
Any alcohol use during pregnancy	42 (32.1)	9 (28.1)	33 (33.3)	0.583	7 (30.4)	35 (32.4)	0.854
Alcohol ≥several times per week prior to pregnancy recognition	37 (28.3)	6 (18.8)	31 (31.3)	0.540	4 (17.4)	33 (30.6)	0.574
Binge episodes prior to pregnancy recognition	35 (26.5)	7 (21.9)	28 (28.0)	0.646	5 (21.7)	30 (27.5)	0.795
Drinks per Wk in Pregnancy							
No Alcohol	91 (68.9)	23 (71.9)	68 (68.0)		16 (69.6)	75 (68.8)	
<1Drink	32 (24.2)	8 (25.0)	24 (24.0)	1.000	6 (26.1)	26 (23.9)	1.000
1-4.9 Drinks	7 (5.3)	1 (3.1)	6 (6.0)		1 (4.4)	6 (5.5)	
≥ 5 Drinks	2 (1.5)	0 (0.0)	2 (2.0)		0 (0.0)	2 (1.8)	
Any alcohol in 3rd trimester	14 (11.1)	1 (3.3)	13 (13.5)	0.185	1 (4.8)	13 (12.4)	0.462
TACE +ve	47 (35.6)	9 (28.1)	38 (38.0)	0.398	6 (26.1)	41 (37.6)	0.346

*Subjects were categorized by FAEE concentration with all subjects with FAEE ≥ LOD compared to all subjects with FAEE < LOD and all subjects with FAEE ≥ 500 ng/g compared to all subjects with FAEE < 500 ng/g.

4.2.4 Perinatal Characteristics of Women and Children

Perinatal, labor and birth characteristics of women and children by FAEE group are summarized in Table 4.17. Children with FAEEs above the limit of detection were more likely to have Apgar scores <7 at 1 minute (18.5% versus 5.3%, p-value 0.043) and a similar pattern was seen with a cut off for FAEE of 500 ng/g. There was a tendency towards lower birth weigh, lower birth length, male sex, and PROM in the FAEE positive groups that did not reach statistical significance. Only 2 of the subjects in the study had gestational diabetes during pregnancy.

Table 4.17. Perinatal, labor, and birth characteristics of women and children in the MEC Follow up Study dichotomized by FAEE concentration ≥ LOD or ≥ 500 ng/g

Characteristic	All Subjects	FAEE ≥ LOD*			FAEE ≥ 500 ng/g*		
	N=132 n (%)	+ve N=32 n (%)	-ve N=100 n (%)	p value exact	+ve N=23 n (%)	-ve N=109 n (%)	p value exact
Birth weight (g)	3472.9 (38.0)	3374.7 (371.4)	3482.0 (423.8)	0.226	3339.0 (385.6)	3479.4 (415.7)	0.167
Birth length (cm)	52.2 (2.3)	51.3 (2.0)	52.4 (2.4)	0.071	51.7 (2.0)	52.4 (2.4)	0.205
Male infant	61 (48.4)	18 (60.0)	43 (44.8)	0.209	12 (57.1)	49 (46.7)	0.475
Preterm delivery (37 weeks)	11 (9.3)	3 (10.3)	8 (9.0)	1.000	3 (15.0)	8 (8.2)	0.395
Vaginal delivery	94 (74.6)	24 (80.0)	70 (72.9)	0.737	18 (85.7)	76 (72.4)	0.521
Gestational Diabetes/ Hyperglycemia Positive	2 (1.5)	0 (0.0)	2 (2.0)	1.000	0 (0.0)	2 (1.8)	1.000
Apgar scores at 1 minute <7	10 (8.3)	**5 (18.5)**	**5 (5.3)**	**0.043**	3 (16.7)	7 (6.8)	0.169
PROM**	13 (10.7)	6 (22.2)	7 (7.5)	0.070	4 (22.2)	9 (8.7)	0.103
Narcotic given during labour	32 (26.5)	9 (33.3)	23 (24.5)	0.458	7 (38.9)	25 (24.3)	0.246

*Subjects were categorized by FAEE concentration with all subjects with FAEE ≥ LOD compared to all subjects with FAEE < LOD and all subjects with FAEE ≥ 500 ng/g compared to all subjects with FAEE < 500 ng/g.

**Premature Rupture of Membranes (PROM).

4.2.5 Maternal and Child Characteristics at Time of Follow up

The maternal and child characteristics at time of follow up for paediatrician visits and by Child History Form by FAEE group are summarized in Tables 4.18. At 12 months of age children with FAEEs above the LOD and ≥500 ng/g were approximately 600g smaller (9.36 kg versus 9.95 kg, p value 0.030). Statistical differences in weight, length and head circumference between FAEE groups were not seen at other time points but there was a tendency for lower weight in the FAEE positive groups (data not shown). Children in the FAEEs above the LOD and ≥500 ng/g groups had a later age of rolling from back to front (5.5 months versus 4.4 months, p-value 0.005) and there was a tendency for an approximate one month delay for FAEE positive groups in crawling, pulling to sitting, and walking unassisted that did not reach statistical significance. There were no evidence of differences in current prescription medicine use, referral for hearing or vision testing, referral for speech therapy, and referral for physiotherapy (data not shown). In addition, there was no difference in parent history of daydreaming, difficulty with academic subjects and speech or behavior problems (data not shown).

On pediatric exam there was no evidence of difference in report of dysmorphic features or concerns about gross motor, fine motor or developmental delay. There was no evidence of differences between groups in weight, height and head circumference percentiles at 2 years of age. There was no evidence of differences on the Nurturance Inventory (data not shown). Report of alcohol use during pregnancy ascertained at 2 years of age was greater than that documented on the CPC 1, 2 and 3 questionnaires with 44.8% of women reporting some alcohol use (including prior to pregnancy recognition).

Table 4.18. Characteristics of women and children in the MEC Follow up Study dichotomized by FAEE concentration ≥ LOD or ≥ 500 ng/g as determined by data collected at 2 year follow up

Characteristic	All Subjects	FAEE ≥ LOD*			FAEE ≥ 500 ng/g*		
	N=132 n (%)	+ve N=32 n (%)	-ve N=100 n (%)	p value exact	+ve N=23 n (%)	-ve N=109 n (%)	p value exact
Weight (kg) 12 months**	9.80 (1.00)	**9.36(0.7)**	**9.95 (1.1)**	**0.030**	**9.30 (0.74)**	**9.92 (1.07)**	**0.045**
Immunizations up to date	108 (91.5)	26 (89.7)	82 (92.1)	0.706	18 (90)	90 (91.8)	0.677
Parent reported Allergies	9 (7.8)	1 (3.7)	8 (9.1)	0.683	1 (5.6)	8 (8.3)	1.000
Medications	14 (11.9)	3 (10.3)	11 (12.4)	1.000	2 (10.0)	12 (12.2)	1.000
Frequent ear infections	14 (11.9)	2 (6.9)	12 (13.5)	0.513	1 (5.00)	13 (13.3)	0.459
English main language in home	111 (95.7)	25 (92.6)	86 (96.6	0.412	17 (94.4)	94 (95.9)	0.577
Milestones (Parental Report)							
Rolled back to front (months)	4.7 sd 4.4	**5.5 sd 1.9**	**4.4 sd 1.4**	**0.005**	**5.7 sd 2.0**	**4.5 sd 1.4**	**0.028**
Pulled to sitting (months)	6.9 sd 4.0	7.6 sd 3.4	6.7 sd 1.5	0.248	7.9 sd 4.0	6.7 sd 1.5	0.252
Crawled (months)	8.4 sd 2.3	9.0 sd 3.3	8.1 sd 1.7	0.208	9.6 sd 3.7	8.1 sd 1.6	0.093
Walked unassisted (months)	12.3 sd 2.3	13.0 sd 3.1	12.1 sd 1.9	0.159	13.2 sd 2.3	12.1 sd 2.0	0.152
Maternal History							
Mother reports depression in last 2 years	34 (25.8)	6 (26.1)	28 (25.7)	1.000	8 (25.00)	26 (26.0)	1.000
Drank Alcohol during pregnancy†	52 (44.8)	12 (41.4)	40 (46.0)	0.830	9 (45.0)	43 (44.8)	1.000
Smoked during pregnancy	13 (11.0)	2 (6.9)	11 (12.4)	0.516	1 (5.0)	12 (12.2)	0.694

*Subjects were categorized by FAEE concentration with all subjects with FAEE ≥ LOD compared to all subjects with FAEE < LOD and all subjects with FAEE ≥ 500 ng/g compared to all subjects with FAEE < 500 ng/g.

**Weight only available for 98 children at 12 months of age.

†Includes prior to pregnancy recognition

4.2.6 Standardized Assessments of Mothers

The results of standardized assessments of mothers by FAEE group are summarized in Table 4.19. A histogram of maternal IQ by FAEE≥ LOD group is presented in Figure 4.10. Sample size for the WASI was 123 with 32 subjects in the FAEE ≥ LOD group and 91 in the FAEE < LOD group. Sample size was 132 for all remaining self-report questionnaires. Maternal IQ was normally distributed for both groups and the mean IQ of all mothers was 113.4 (SD 10.6). Seven mothers (5%) had an IQ greater than 130. On box plot three outliers below 90 (83 to 87) and one outlier at 138 were identified (data not shown). These were included in analyses; no difference was observed if they were excluded from analyses. There was no evidence of differences by FAEE group for maternal IQ, home environment assessment (Home Screening Questionnaire), and Parent Satisfaction Scale (PSS) Standard Scores of Spouse, Parent-Child Relationship, Parenting Performance and Total satisfaction. There was also no evidence of differences between groups if subjects were categorized as being below the 25^{th} percentile on the PSS.

There was no evidence of differences by FAEE group on the Family Assessment Device General Functioning, Behavior Control, Affective Involvement, Affective Responsiveness, Roles, Communication, and Problem Solving Scores when examined as continuous variables and when categorized as being below the 25^{th} percentile (data not shown).

Table 4.19. Results of standardized assessments of women in the MEC Follow up Study dichotomized by FAEE concentration ≥ LOD or ≥ 500 ng/g for 132 MEC Follow up Study Participants at 2 years of age

Characteristic	All Subjects	FAEE ≥ LOD*			FAEE ≥ 500 ng/g*		
	N=132 n (%)	+ve N=32 n (%)	-ve N=100 n (%)	p value exact	+ve N=23 n (%)	-ve N=109 n (%)	p value exact
WASI**							
Verbal IQ	108.6 sd 10.9	107.7 sd 11.6	108.9 sd 10.8	0.619	105.8 sd 10.9	109.2 sd 11.1	0.207
Performance IQ	115.4 sd 10.8	116 sd 10.6	115.2 sd 10.9	0.726	116.1 sd 10.0	115.2 sd 11.0	0.743
Full-4 IQ	113.4 sd 10.6	113.2 sd 10.7	113.5 sd 10.6	0.910	112.0 sd 8.8	113.7 sd 10.9	0.500
Home Screening Questionnaire							
Suspect	21 (16.3)	3 (9.7)	18 (18.4)	0.402	2 (9.1)	19 (17.8)	0.526
Parent Satisfaction Scale Standard Scores							
Spouse Satisfaction	57.7 sd7.0	57.6 sd 6.6	57.7 sd 7.2	0.932	57.8 sd 7.3	57.8 sd 6.9	0.645
Parent-Child Relationship	55.9 sd 9.0	57.9 sd 9.3	55.3 sd 8.8	0.159	57.5 sd 10.3	55.6 sd 8.6	0.362
Parenting Performance	55.0 sd 10.2	57.5 sd 10.8	54.2 sd 10.0	0.133	57.3 sd11.7	54.5 sd 9.9	0.256
Total PSS	58.0 sd 9.0	58.6 sd 9.8	57.8 sd 8.8	0.691	57.7 sd 11.1	58.1 sd 8.6	0.844
Family Assessment Device							
General Functioning	19.0 sd 5.0	18.5 sd 4.7	19.2 sd 5.0	0.505	18.3 sd 5.0	19.2 sd 5.0	0.450

*Subjects were categorized by FAEE concentration with all subjects with FAEE ≥ LOD compared to all subjects with FAEE < LOD and all subjects with FAEE ≥ 500 ng/g compared to all subjects with FAEE < 500 ng/g.

**N for WASI was 123 with 32 subjects in the FAEE ≥LOD group and 91 in the FAEE < LOD group. N for the WASI was lower as some subjects only completed the self-report portion of the MEC Follow Up Study.

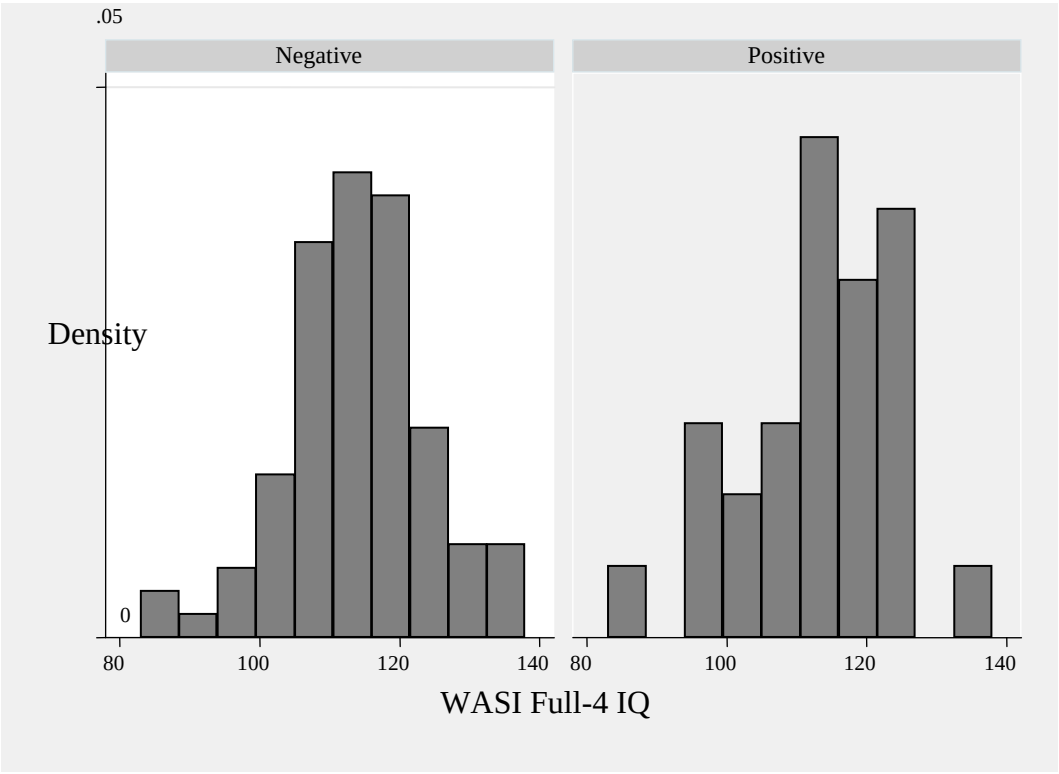


Figure 4.10. Histogram of maternal IQ (WASI Full 4-Scale IQ) by FAEE concentration ≥ LOD (n=123)

4.2.7 BSID-II and CBCL Assessments of Children

The results of BSID-II and CBCL assessments of children by FAEE group are summarized in Tables 4.20 and 4.21. Histograms of Mental and Psychomotor Development Indices by FAEE concentration above the LOD are presented in Figures 4.11 and 4.12 and reveal normal distributions. Sample size for the BSID-II was 123 with 32 subjects in the FAEE ≥ LOD group and 91 in the FAEE < LOD group as some subjects only completed self-report questionnaires and were not assessed by psychologist. Sample size for self-report questionnaires was 132. There were 4 subjects who could not be assigned a specific continuous value on the BSID-II MDI and PDI due to non-compliance with testing. The mean MDI for the group was 101.5 with a mean PDI of 93.7. On box plot two outliers were identified in the FAEE negative group on the MDI with scores below 70 (54 and 68) (data not shown). These children had significant medical complications in the first year of life. One child had idiopathic thrombocytopenic purpura (ITP) at 9 months of age with evidence of intracranial haemorrhage and subsequent long term corticosteroid use. The other child had a near drowning and has lasting cognitive deficits. The child with ITP also had the only outlying value of 60 on the PDI. Analyses were performed including and excluding these subjects with no statistical differences in results.

Children with FAEE ≥ 500ng/g had a PDI 7.1 points (87.9 versus 95.0, p value 0.009) lower than unexposed children. There were also differences when children were categorized as delayed on the PDI with 50.0% of children with FAEE ≥ 500 ng/g delayed versus 17.2% (p value 0.007) of unexposed children. There was no evidence of differences between groups on the MDI. There was also no evidence of differences

between FAEE groups by standard score and referral cut off on CBCL sub-scales of Oppositional Defiant Disorder, Attention Deficit Hyperactivity Disorder, Affective Problems, External Problems, and Aggressive Problems (data not shown).

There was no evidence of differences on the BSID-II MDI and PDI by maternal report of alcohol use at any point in time or T-ACE score or by any method of categorising alcohol use other than reported use of daily alcohol use prior to pregnancy recognition (data not shown).

Table 4.20. Results of BSID-II and CBCL assessments dichotomized by FAEE concentration ≥ LOD or ≥ 500 ng/g for 132 MEC Follow up Study Participants at 2 years of age

Characteristic	All Subjects	FAEE ≥ LOD*			FAEE ≥ 500 ng/g*		
	N=132 n (%)	+ve N=32 n (%)	-ve N=100 n (%)	p value exact	+ve N=23 n (%)	-ve N=109 n (%)	p value exact
BSID-II**							
Mental Development Index	101.5 sd 12.0	101.5 sd 12.0	101.6 sd 1.3	0.988	99.3 sd 12.2	102.1 sd 11.9	0.324
Mental Score Delayed	10 (8.9)	3 (11.1)	7 (8.2)	0.702	3 (15.0)	7 (7.6)	0.380
Psychomotor Development Index	**93.7 sd 12.6**	**90.9 sd 14.6**	**94.6 sd 11.9**	**0.177**	**87.9 sd 13.4**	**95.4 sd 11.6**	**0.009**
Psychomotor Score Delayed	**27 (23.5)**	**12 (41.4)**	**15 (17.4)**	**0.009**	**11 (50.0)**	**16 (17.2)**	**0.001**
CBCL Standard Scores							
Average Phrase Length <25%ile	20 (19.0)	3 (13.0)	17 (20.7)	0.553	2 (13.3)	18 (20.0)	0.731
Total Words <25%ile	22 (17.5)	4 (14.3)	18 (18.4)	0.781	3 (15.0)	19 (17.9)	0.752
PDD Problem‡	52.5 sd 5.4	50.9 sd 1.6	52.9 sd 6.0	0.003	51.0 sd 1.8	52.8 sd 5.8	0.109
PDD Referral‡†	8 (6.25)	0 (0.0)	8 (8.2)	0.197	0 (0.0)	8 (7.6)	0.349
Anxiety Problem	52.0 sd 3.9	51.0 sd 1.9	52.3 sd 4.3	0.090	51.0 sd 1.8	52.2 sd 4.1	0.156
Anxiety Referral†	11 (8.6)	0 (0.0)	11 (11.2)	0.066	0 (0.0)	11 (10.4)	0.209
Internal Problem	44.1 sd 8.7	41.7 sd 8.1	44.7 sd 8.7	0.081	41.2 sd 8.1	44.7 sd 8.7	0.085
Internal Referral†	7 (5.5)	0 (0.0)	7 (7.1)	0.198	0 (0.0)	7 (6.6)	0.603
Sleep Problem	54.2 sd 7.6	53.0 sd 5.9	54.6sd 8.1	0.312	53.7 sd 5.5	54.6 sd 8.0	0.295
Total Problems	46.0 sd9.2	43.6 sd 9.1	46.8 sd 9.1	0.101	42.7 sd 10.3	46.7 sd 8.8	0.059
Total Problem Referral†	9 (7.0)	2 (6.7)	7 (7.1)	1.000	2 (9.1)	7 (6.6)	0.652

*Subjects were categorized by FAEE concentration with all subjects with FAEE ≥ LOD compared to all subjects with FAEE < LOD and all subjects with FAEE ≥ 500 ng/g compared to all subjects with FAEE < 500 ng/g.

**N for BSID-II was 119 with 30 subjects in the FAEE ≥ LOD group and 89 in the FAEE < LOD group due to non-compliance with testing or participation in only the self-report portion of the MEC Follow Up Study.

†'Referral' refers to a T score of ≤60 on the domains of the CBCL which are within the borderline/clinical referral range-higher scores represent more 'deviant' behavior.

‡PDD = Pervasive Developmental Delay at age of follow up

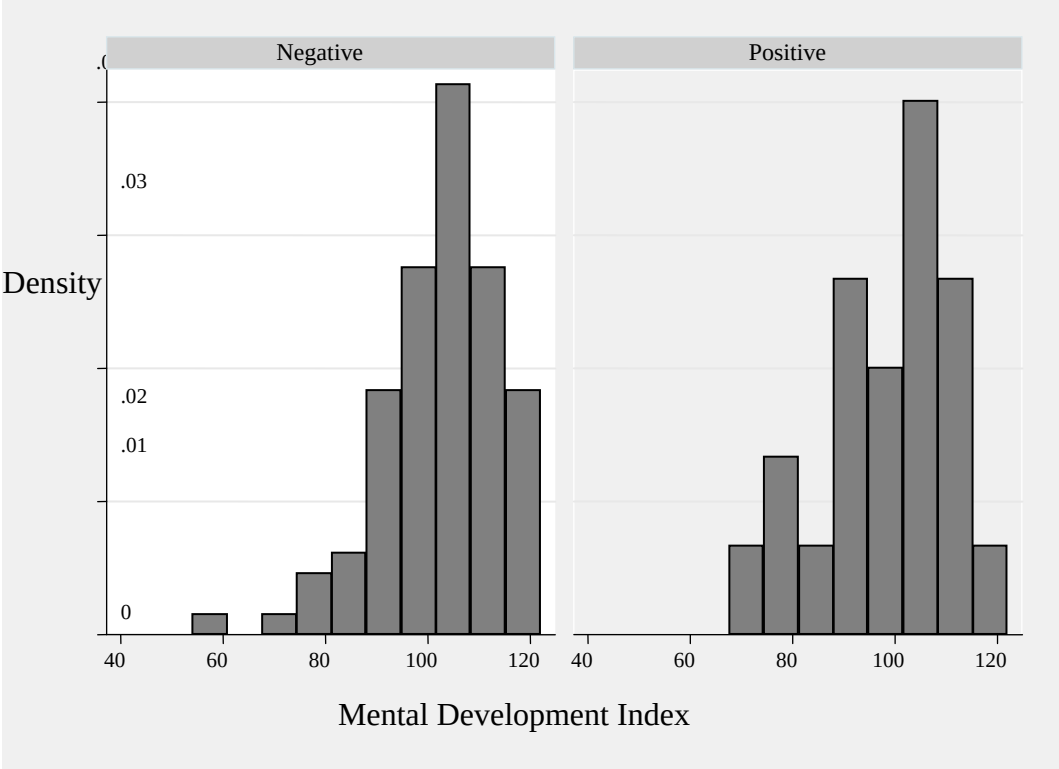


Figure 4.11. Histogram of BSID-II Mental Development Index by FAEE concentration greater than the LOD (n=119)

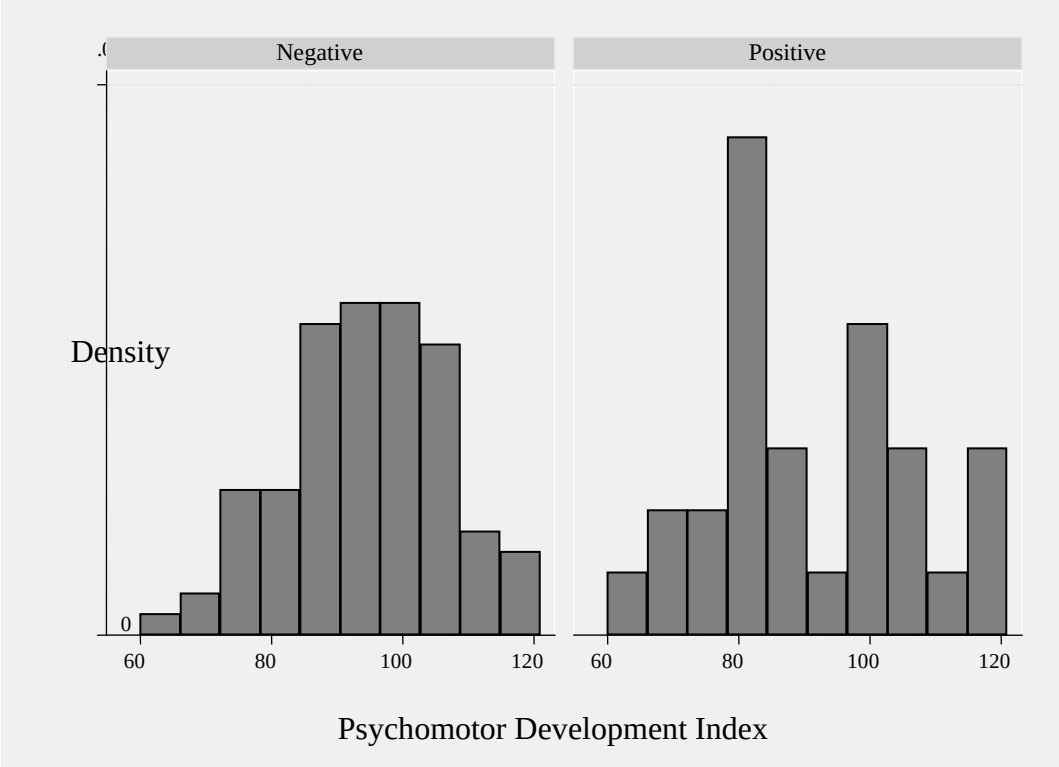


Figure 4.12. Histogram of BSID-II Psychomotor Development Index by FAEE concentration greater than the LOD (n=119)

4.2.8 Standardized Parental-Report Assessments of Children

The results of ABAS, TABS, ASQ and NDDS by FAEE group are summarized in Table 4.21. There was a tendency, that did not reach significance, for FAEE positive subjects to have a lower ABAS GAC Composite score (93.8 versus 98.4, p value 0.146), lower ABAS Conceptual Composite Scores (93.2 versus 98.7. p-value 0.228), and lower ABAS Practical Composite (84.3 versus 91.4, p-value 0.121. This was also seen when subjects were categorized as ‘Below Average’ by test score.

No differences were seen between FAEE groups on the TABS overall score and domain scores. There was also no evidence of differences between groups on the Ages and Stages Questionnaire and Nippissing District Developmental Screener.

Table 4.21. Results of the ABAS, TABS, and NDDS dichotomized by FAEE concentration ≥ LOD or ≥ 500 ng/g for 132 MEC Follow up Study Participants at 2 years of age

Characteristic	All Subjects	FAEE ≥ LOD*			FAEE ≥ 500 ng/g*		
	N=132 n (%)	+ve N=32 n (%)	-ve N=100 n (%)	p value exact	+ve N=23 n (%)	-ve N=109 n (%)	p value exact
Adaptive Behavior Assessment System (ABAS)							
Composite Score	97.3 sd 15.1	93.8 sd 15.1	98.4 sd 15.0	0.146	93.2 sd 16.4	98.1 sd 14.8	0.169
Conceptual Score	97.3 sd 22.4	93.2 sd 23.4	98.7 sd 22.0	0.228	92.7 sd 26.8	98.3 sd 21.2	0.275
Social Score	95.7 sd 22.3	93.4 sd 25.4	96.4 sd 21.3	0.514	91.4 sd 29.0	96.6 sd 20.6	0.420
Practical Score	90.1 sd 19.5	86.3 sd 20.0	91.4 sd 19.3	0.203	84.3 sd 22.5	91.4 sd 18.7	0.121
Composite Score Below Average	31 (25.4)	10 (33.3)	21 (22.8)	0.334	7 (33.3)	24 (23.8)	0.411
Conceptual Below Average	24 (19.2)	8 (25.8)	16 (17.0)	0.300	6 (27.3)	18 (17.5)	0.370
Social Below Average	24 (18.8)	7 (22.6)	17 (17.5)	0.598	5 (22.7)	19 (17.9)	0.561
Practical Below Average	53 (41.7)	14 (46.7)	39 (40.2)	0.531	10 (47.6)	43 (40.6)	0.631
Temperament and Atypical Behavior Scale (TABS)							
Standard Score	96.1 sd 16.0	96.0 sd 17.3	96.2 sd 15.7	0.970	98.3 sd 18.2	95.6 sd 15.6	0.474
Dysregulated Score	47.0 sd 8.9	46.3 sd 9.5	47.2 sd 8.7	0.587	48.6 sd 8.8	46.6 sd 8.9	0.337
Nippissing District Developmental Screener (NDDS)							
≥ 2+ Referral Suggested	11 (8.5)	2 (6.5)	9 (9.1)	1.000	2 (8.7)	9 (8.4)	1.000
Ages and Stages Questionnaire (ASQ)							
Communication Below Average	11 (8.8)	3 (9.7)	8 (8.5)	1.000	2 (9.1)	9 (8.7)	1.000
Gross Motor Below Average	7 (5.6)	3 (9.7)	4 (4.3)	0.606	2 (9.1)	5 (4.9)	0.606
Fine Motor Below Average	9 (7.2)	2 (6.4)	7 (7.5)	1.000	1 (4.6)	8 (7.8)	1.000

*Subjects were categorized by FAEE concentration with all subjects with FAEE ≥ LOD compared to all subjects with FAEE < LOD and all subjects with FAEE ≥ 500 ng/g compared to all subjects with FAEE < 500 ng/g.

4.2.9 Spearman Correlation of Bayley Scales of Infant Development Indices with Subject Characteristics

BSID-II PDI was weakly positively correlated with adaptive function while it was weakly negatively associated with FAEE concentration (Table 4.22). BSID-II MDI was weakly positively correlated with adaptive function and maternal IQ but there was no evidence of correlation with FAEE concentration (Table 4.23).

BSID-II PDI and MDI were not significantly correlated with maternal, infant, psychosocial, and home environment characteristics (data not shown).

Table 4.22. Spearman Correlations of Prenatal, Birth and Developmental Outcomes with Bayley Scales of Infant Development Psychomotor Development Index for 119 MEC Follow up Study Participants at 2 years of age

Characteristic	rho	P Value
FAEE level	-0.2045	0.0270
ABAS - GAC	0.3768	0.0001
Maternal age at time of birth	-0.1326	0.1691

Table 4.23. Spearman Correlations of Prenatal, Birth and Developmental Outcomes with Bayley Scales of Infant Development Mental Development Index for 119 MEC Follow up Study Participants at 2 years of age

Characteristic	rho	P Value
FAEE level	-0.0022	0.9813
ABAS - GAC	0.3012	0.0016
Maternal age at time of birth	0.0042	0.9653
Maternal IQ (WASI)	0.2495	0.0086

4.2.10 Multivariate Logistic Regression Analysis

A parsimonious logistic regression model was developed with an outcome of delay or significant delay on the BSID-II Psychomotor Development Index (Table 4.24). The final model has an overall pseudo R^2 of 0.324. In this model female sex was a protective factor while FAEE concentration, daily alcohol use prior to pregnancy recognition, and maternal age greater than 35 years of age at time of delivery were risk factors for delay on the PDI of the BSID-II. Birth weight was controlled for in the model and the effect of FAEE group on PDI remained significant and relatively unchanged in models that included birth weight and models that did not. This would seem to indicate that in this sample the negative effects associated with elevated FAEE do not appear to be mediated through lower birth weight. Variables in the domains of maternal characteristics (e.g., maternal age, maternal intelligence, maternal education, self-reported household income, marital status, food and housing security) mental health (e.g., maternal history of depression), lifestyle (e.g., maternal cigarette use and diet), psychosocial factors (e.g., parenting satisfaction, and maternal history of abuse), drug and alcohol use prior, during and after pregnancy, T-ACE questionnaire score, and child characteristics (e.g., gestational age and head circumference) were included in initial models but only the parsimonious model is presented. Women who reported daily alcohol use prior to pregnancy recognition were all in the FAEE negative group.

Separate models were also developed using dichotomous FAEE cut offs of ≥ LOD (AOR 3.05, 95%CI 1.02 – 9.11), 500 ng/g (AOR 5.82, 95% CI 1.71 – 19.81), 1,000 ng/g (AOR 8.51, 95% CI 2.29 – 27.87), 5,000 ng/g (AOR 26.92, 95% CI 3.36 – 215.47) and 10,000 ng/g (AOR 28.51, 95% CI 2.21 – 368.03).

A logistic regression model with an outcome of delay or significant delay on the BSID-II Mental Development Index was not developed as there were no significant associations on univariate analysis.

Diagnostic test parameters for FAEE in meconium as a predictor of motor delay at 2 years of age were generated. Using cut offs of FAEE ≥ LOD, 500 ng/g, 1,000 ng/g, 5,000 ng/g and 10,000 ng/g independently and in combination with daily report of alcohol use prior to pregnancy recognition the following test parameters were obtained: sensitivity of 53.6% (Daily alcohol use prior to pregnancy recognition + FAEE ≥ LOD), specificity 97.7% (FAEE ≥ 10,000 ng/g), positive predictive value (PPV) 70.0% (Daily alcohol use prior to pregnancy recognition + FAEE ≥ 10,000 ng/g), and negative predictive value (NPV) of 81.6% (Daily alcohol use prior to pregnancy recognition + FAEE ≥ 500 ng/g).

An area under the receiver operator curve (ROC) of 0.63 (95% CI, 0.52 – 0.74) was obtained for FAEE concentration as a continuous variable and motor delay on the BSID-II (Figure 4.13).

Table 4.24. Adjusted odds ratios for child and maternal characteristics and FAEE concentration for subjects assessed as being delayed or severely delayed on the BSID-II Psychomotor Development Index for MEC Follow up Study Participants at 2 years of age

Characteristic	**Delayed (n=29) n (%)**	**WNL* (n=90) n (%)**	**AOR (95% CI)**
Infant Characteristics			
Female Sex	9 (31.0)	50 (58.1)	0.08 (0.02-0.33)
Birth weight (grams)			1.00 (0.99-1.00)
Lifestyle			
Daily Alcohol use prior to pregnancy recognition	3 (10.0)	1 (1.1)	26.95 (1.91 – 380.05)
FAEE			
Below the limit of detection	17 (59.0)	71 (80.7)	1.00
500 – 1,000 ng/g	3 (10.3)	7 (7.9)	1.30 (0.22 – 7.77)
1,000 – 5,000 ng/g	3 (10.3)	4 (4.6)	2.42 (0.33-18.00)
5,000 – 10,0000 ng/g	2 (6.9)	1 (1.1)	18.26 (0.97- 342.71)
≥10,000 ng/g	4 (13.8)	2 (2.3)	39.41 (2.73 –569.00)
Maternal Characteristics			
Age 35 or greater at time of delivery	22 (75.9)	49 (55.7)	3.00 (0.88-10.30)

*WNL Within Normal Limits

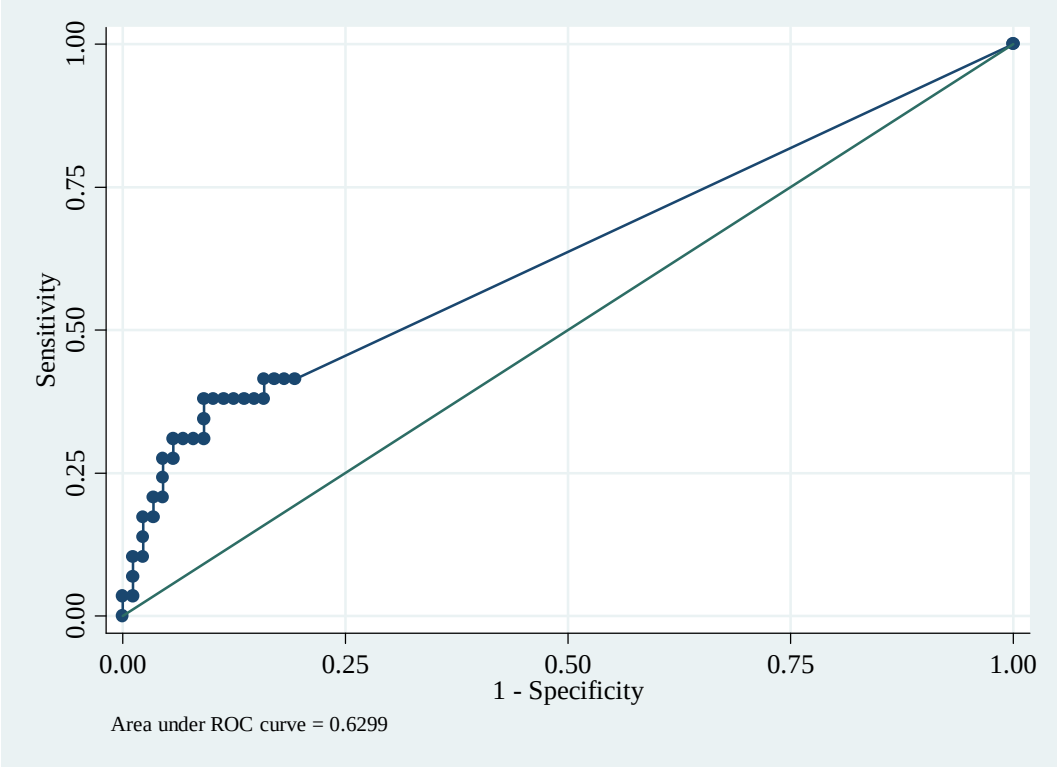


Figure 4.13. Receiver operating curve for FAEE concentration as a predictor of motor delay as determined by the Psychomotor Development Index of the BSID-II for subjects of the Meconium Follow up Study

4.2.11 Multivariate Linear Regression Analysis

Parsimonious linear regression models were developed for BSID-II Psychomotor and Mental Development Indices. Assumptions of normality, linearity, independence and equal variance were assessed and confirmed with scatter plots of residuals versus predicted values, histograms of residuals, and scatter plots of residuals versus each independent variable. For the BSID-II Psychomotor Development Index a final model was developed with an overall R-squared of 0.135 (Table 4.25). The equation for the model is as follows:

BSID-II Psychomotor Development Index = 84.2 – (8.8*FAEE ≥ 500ng/g) + (6.8*Female Sex) – (14.2*Daily Alcohol prior to pregnancy recognition) +

For the BSID-II Mental Development Index a final model was developed with an overall R-squared of 0.190 (Table 4.26). Alcohol and drug related variables did not remain in the final model. The equation for the model is as follows:

BSID-II Mental Development Index = 57.0 + (5.7*Female Sex) - (4.7*Maternal Age ≥35 years of age) + (0.3*Maternal IQ) + (5.5*Income≥$60,000per year)

Table 4.25. Factors associated with the Bayley Scales of Infant Development Psychomotor Development Index in the MEC Follow up Study in multiple linear regression

Variables	Coefficient	95% CI	P value
Infant Characteristics			
Female Sex	6.83	2.42 – 11.23	0.003
Lifestyle			
Daily Alcohol use prior to pregnancy recognition	-14.20	-26.22 - -2.16	0.021
FAEE ≥5,000 ng/g	-8.76	-16.93 - -0.58	0.036
Constant	74.67	63.50 – 85.85	<0.001

Table 4.26. Factors associated with the Bayley Scales of Infant Development Mental Development Index in the MEC Follow up Study in multiple linear regression

Variables	Coefficient	95% CI	P value
Infant Characteristics			
Female Sex	5.69	1.18 – 10.20	0.014
Maternal Characteristics			
Maternal age ≥35 years	-4.65	-9.25 - -0.06	0.047
Income ≥ $60,000/year	5.46	-0.24 – 11.17	0.060
Maternal IQ	0.30	0.08 – 0.52	0.007
Constant	57.04	32.44 – 81.63	<0.001

4.3 Maternal Willingness to Consent to Drug and Alcohol Screening of their Newborns

4.3.1 Focus Groups

Focus groups were held with 29 women from the Calgary Urban Projects Society (CUPS), CUPS One World, and the community. Participants ranged from 18 to 40 years of age with the highest level of education achieved ranging from Grade 9 to a Masters degree. Focus groups included women who had experienced child apprehension as a result, from their perspective, of positive drug tests. A breakdown of themes from the focus groups is presented in Appendix C in the terms and headings of the Health Belief Model.

Key themes identified in the focus groups included: justice, all women should be tested without discrimination; women need consistent support and information during pregnancy; perceived barriers to testing include fear of apprehension and potential harm to mother and child; and perceived benefits of testing include decreased incidence of exposure with an accompanying decrease in costs associated with fetal alcohol spectrum disorders, best chance for baby, and an opportunity to change. Focus group results suggested an acceptance for universal testing with the condition that a positive drug or alcohol test should not be used as evidence for child apprehension.

The overriding theme that was consistent across all focus groups was that “all babies should be tested if it makes a difference”. This included women whose children had been apprehended, in their perception, due to positive drug tests. They supported universal testing without consent or opt-out consent. However, they did say that if consent is obtained then it should be written consent. This is in the context of a trusting

relationship with a care-provider so that they can talk about health issues. In addition, women told us that all women should be effectively screened at their first prenatal visit so that they can receive treatment during pregnancy. At the same time al women should be presented with information about healthy pregnancies and drug and alcohol at the first prenatal visit. Regarding inconsistent messages from care-providers, media, and support people, woman commented that they did not want to hear that it was ok to smoke, drink or use drugs during pregnancy. Inconsistent messages confused women and ‘gave them permission’ to use. In addition, women felt that with support prior to and during pregnancy that screening would almost be unnecessary.

Women said that a positive test result should not automatically result in an apprehension – “Mom’s should be given a trial period with their babies”. During that time a mother should have access to supports, resources, rehabilitation, and counselling. Mothers and babies identified at risk should be closely monitored. Finally the women in the focus groups expressed tremendous frustration and hurt with the perceived injustice of current ‘targeted’ screening methods.

4.3.2 Questionnaires on Post-partum Units

4.3.2.1 Participation Rates

The cross-sectional survey was administered to 1509 women (78.4% of those eligible) on postpartum units in an urban health region in Canada serving a population of 1,051,870 (Table 4.27) (299). There were 14,473 live births in 2003 in the Calgary Health Region and the survey represents a sample of approximately 13% of all live births for the year 2003. Based on admission logs 3253 women were admitted to postpartum units during the data collection period. Of those admitted, 1920 (59%) were eligible to participate. Reasons for ineligibility, in order of frequency, included early discharge, or admission to unit and subsequent discharge between 4:30 pm and 8 am the next morning (41.1%), language barrier (26.5%), medical/neonatal complications (7.3%), antepartum (12.5%), and under age (1.3%) . Of the 1509 women that agreed to participate 1474 (97.7%) completed the entire questionnaire. Subject fatigue was the main reason identified for not completing the questionnaire.

Table 4.27. Participation rates in the cross-sectional survey by hospital site in the Calgary Health Region (July – October, 2003)

	All Sites N (%)	FMC N (%)	PLC N (%)	RGH N (%)
Total Admissions	3253	928	1052	1273
Ineligible	1333 (41.0)	352 (37.9)	444 (42.2)	537 (42.2)
Eligible	1920 (59.0)	576 (62.1)	608 (57.8)	736 (57.8)
Participation	1509 (78.4)	475 (82.3)	499 (82.1)	535 (72.4)

Table 4.28. Reasons for ineligibility for the cross-sectional survey by hospital site in the Calgary Health Region (July – October, 2003)

	All Sites N (%)	FMC N (%)	PLC N (%)	RGH N (%)
Total ineligible	1333	352	444	537
Early discharge	548 (41.1)	156 (44.3)	132 (29.7)	260 (48.4)
Language	353 (26.5)	44 (12.5)	229 (51.6)	80 (14.9)
Antepartum	166 (12.5)	80 (22.7)	2 (0.5)	84 (15.6)
Neonatal complications	76 (5.8)	17 (4.8)	49 (11.0)	10 (1.9)
Medical	20 (1.5)	10 (2.8)	7 (1.5)	3 (0.5)
<18 years old	17 (1.3)	4 (1.1)	6 (1.3)	7 (1.3)
Other*	153 (11.5)	41 (11.6)	19 (4.3)	93 (17.3)

*Other (In order of frequency): special care nursery, not available, MEC study participant, confidential patient, social services, friend/relative of research assistant, and infant/maternal death.

4.3.2.2 Subject Demographics

Patient demographic characteristics are presented in Tables 4.29 and 4.30. Approximately half of the women were 30 years of age or over (54.2%) with the largest proportions of women in the study between 30-34 (34.1%) and 25-29 (27.9%) years of age. The majority of women were Caucasian (79.0%). Approximately 93% of women were married or in a common law relationship and roughly half of the women (47.1%) were primipara. Forty percent of women had a university degree and 25.2% of the subjects had a high school diploma or lower. Prior to delivery women held positions as: homemakers (21.5%), administrators (7.0%), teacher (6.8%), and financial auditors (4.5%). Subjects reported that 97.6% of their partners had full-time positions.

Table 4.29. Demographic characteristics, including age, ethnicity, marital status and parity of participants (n=1509) in a cross-sectional survey examining factors related to willingness to consent to drug and alcohol screening of infants

	Total (n=1509)
	N (%)
Age	
≥ 30 yrs	**786 (54.2)**
18-19 yrs	42 (2.9)
20-24 yrs	218 (15.0)
25-29 yrs	404 (27.9)
30-34 yrs	495 (34.1)
35-39 yrs	249 (17.2)
40+ yrs	41 (2.8)
Ethnic Background	
Caucasian/White	**1145 (79.0)**
Native/Aboriginal	55 (3.8)
Chinese	50 (3.4)
South Asian	50 (3.4)
Other**	140 (9.7)
Marital Status	
Married or Common Law	**1347 (93.0)**
Married	1152 (79.5)
Common law/live with partner	195 (13.5)
Single (never married)	88 (6.1)
Divorced	4 (0.3)
Separated	8 (0.6)
Widowed	1 (0.1)
Parity (Number of previous births)	
Primipara	**681 (47.1)**
1	503 (34.8)
2	182 (12.6)
3+	81 (5.6)

* Response rates to questions varied from 1450 to 1509.

** Includes, in order of frequency: Latin American, Filipino, African North American/Black, West Asian/Arab, Italian, South East Asian, Japanese, Greek, Korean, Jewish, Hispanic, Russian, Jamaican, African.

Table 4.30. Education and occupation of participants in a cross-sectional survey examining factors related to willingness to consent to drug and alcohol screening of infants

	Total (n=1509)*
	N (%)
Education	
≤ Graduated High School	**365 (25.2)**
Did not graduate High School	78 (5.4)
Graduated High School	287 (19.8)
Some Trade, Technical, Vocational School, Business/Community College, or University	173 (12.0)
Completed Trade, Technical, Vocational School or Business/Community College	330 (22.8)
≥ Completed University Undergraduate Degree	**582 (40.0)**
Completed University Undergraduate Degree	461 (31.8)
Completed Post-Graduate Degree or Professional School	117 (8.1)
Working Status	
Full-time	1207 (84.7)
Occupation	
Homemakers	311 (21.5)
Administrators/Managers	101 (7.0)
Teacher	98 (6.8)
Financial Auditors and Accountants	65 (4.5)
General Clerk	56 (3.9)
Registered Nurse	45 (3.1)
Student	44 (3.0)
Other**	730 (50.2)
Partner's Working Status	
Full-time	1357 (97.6)
Partner's Occupation	
Administrator/Manager	136 (9.6)
Tradesman	118 (8.3)
Engineer	107 (7.5)
Self Employed	58 (4.1)
Financial Auditors and Accountants	42 (3.0)
Construction Trades Helpers and Labourers	35 (2.5)
Sales	34 (2.4)
Student	29 (2.0)
Other†	859 (60.6)

* Response rates to questions varied from 1450 to 1509.

** Includes, in order of frequency: Customer Service Representative, Food and Beverage Server, Early childhood educator, Unemployed, Self Employed, Social Workers, secretaries, cashiers, paralegal and related occupations, physiotherapists, dental assistants, pursers and flight attendants, and nurses aides.

† Includes, in order of frequency: Teacher, computer programmer, Information Systems Analysts and Consultants, Truck Driver Lawyer, Financial and Investment Analysts and Advisors, Other Trades Helpers and Labourers, Sales Representatives, Electronic Service Technicians, Air Pilots, Flight Engineers and Flying Instructors, and Police officers.

4.3.2.3 Lifestyle

A majority of women reported some alcohol use (79.5%) in the 3 months prior to pregnancy with 50.3% of these women reporting a binge episode of 5 or more drinks on one occasion (Table 4.31). Approximately a quarter (27.3%) of women reported smoking cigarettes prior to pregnancy with half this number (13.2%) continuing to smoke during pregnancy.

Type of alcohol consumed, in order of preference, was wine (45.4%), beer (27.9%), mixed drinks (20%), coolers (15.7%), and liquor (14.1%). The same trend for alcohol preference was seen for alcohol use during pregnancy. Half of the women (50.3%) who drank prior to pregnancy, and 39.9% of women overall, reported an episode in which they drank 5 or more drinks in the year prior to pregnancy recognition. Report of alcohol use was examined several ways: 23.7% of women reported alcohol use during pregnancy and 39.2% reported alcohol use prior to pregnancy recognition, and in total 44.5% consumed alcohol during pregnancy. Some women did not define alcohol consumption prior to pregnancy recognition as ‘drinking in pregnancy’. The majority of women who drank alcohol during pregnancy did so in the 1st trimester (90.5%). However, women drank alcohol in other trimesters, with 14.4% in the 2nd, 18.7% in the 3rd, and 7.3% in all 3 trimesters. *T-ACE* – Half of the women (50.1%) who reported alcohol use prior to pregnancy had a positive T-ACE of 2 or greater and 8.5% of women who reported alcohol use had a T-ACE score of 3 or greater. Fully half of the women (49.1%) that reported alcohol use during pregnancy reported a Tolerance of 3 or greater drinks to feel high, resulting in a positive T-ACE, a marker for risk drinking during pregnancy.

Table 4.31. Self-reported lifestyle including tobacco and alcohol use of participants in a cross-sectional survey examining factors related to willingness to consent to drug and alcohol screening of infants

		Total* **(n=1509)**
		N (%)
Tobacco Use		
Smoked cigarettes in the 12 months prior to pregnancy		396 (27.3)
Number of Cigarettes Per Day, ≥10 cigarettes per day		184 (46.6)
Smoked cigarettes during this pregnancy		191 (13.2)
Number of Cigarettes Per Day, ≥10 cigarettes per day		45 (23.6)
Alcohol Use		
Drank alcohol in the 12 months prior to pregnancy		1153 (79.5)
Type of Alcohol	**Wine**	658 (45.4)
	Beer	404 (27.9)
	Mixed Drinks/ Cocktails	290 (20.0)
	Coolers	227 (15.7)
	Liquor	204 (14.1)
Drank 5 or more drinks on one occasion in the 12 months prior to pregnancy	**Of women who drank prior to pregnancy**	578 (50.3)
	Of all women	578 (39.9)
Alcohol Use During Pregnancy		
Drank alcohol during pregnancy &/or before knowledge of pregnancy		**634 (44.5)**
Drank alcohol during pregnancy		343 (23.7)
Drank alcohol before knowledge of pregnancy but while pregnant		558 (39.2)
Did not believe they drank during pregnancy but drank before knowledge of pregnancy		**289 (20.3)**
Type of Alcohol (among women that reported alcohol use)	**Wine**	332 (52.5)
	Beer	180 (28.5)
	Mixed Drinks/ Cocktails	104 (16.5)
	Coolers	81 (12.8)
	Liquor	58 (9.2)
Trimester of Alcohol Use Among Women that drank during pregnancy		
Any 1st trimester use		572 (90.5)
Any 2nd trimester use		91 (14.4)
Any 3rd trimester use		118 (18.7)
All 3 trimesters		46 (7.3)
T-ACE		
T-ACE ≥2 among women that reported any alcohol use prior to pregnancy		540 (50.1)
T-ACE ≥2 among all women		540 (37.2)

*Actual number of respondents varied between 1424-1509.

4.3.2.4 Prenatal Care/Support

In general, women reported that care providers asked about their alcohol and drug use during pregnancy (83.5%) with 64.2% of physicians who discussed alcohol use recommending ‘none is best’ (Appendix C). Some care providers (7.9%) gave advice related to alcohol use that is not in keeping with the current North American guidelines of ‘no alcohol is best’. Approximately 10% of women believed that some alcohol use during pregnancy was appropriate. Only 38.9% of participants felt that women were aware of the potential problems for children exposed to alcohol use during pregnancy and there was limited interest in additional information about alcohol (7.2%) and smoking (6.5%). 9.3% felt that care-providers can predict who used drugs or alcohol during pregnancy based on patient demographic characteristics (e.g., ethnicity, age, occupation). Participants felt that a woman should receive information about any sort of screening for drug or alcohol use at her first prenatal visit (99.7%) and prior to sample collection (96.3%).

Women felt supported during pregnancy with care providers (99.0%) and spouse identified as sources of support (96.9%) (data not shown). Women felt that they received enough information during pregnancy but were interested in additional information about stress (44.1%), over the counter drugs (43.5%), pregnancy related medical complications (43.0%), and exercise (34.6%) (data not shown). Women were not interested in additional information about alcohol (7.2%) and smoking (6.5%). Leading sources of information regarding alcohol and drug use during pregnancy included books (88.7%), physicians (79.2%), media or TV (78.3%) and the Calgary Health Region’s Maternity information

booklet, “From Here Through Maternity” (76.9%) (data not shown). A majority of women (81.8%) felt that information sources had consistent messages.

4.3.3 Agreement with Screening of Infants and Self-reported Alcohol Use

Women's opinions of alcohol and drug testing and their willingness to consent to testing of their infant by self-report of alcohol use during pregnancy are presented in Table 4.32. Approximately half (57.7%) of the women supported a program in which women could refuse testing. A program in which no consent was obtained had more support (68.6%) and the majority of women agreed that they would consent to the testing of their infant (93.8%). The majority of participants felt that before consenting to testing a woman would need to know what happens with a positive test result (97.1%), who has access to the information (93.4%), how effective medical care is for the child (97.4%), and the chance that a baby with a positive test would have a problem (98.1%). Women who reported alcohol use during pregnancy were more likely to:

a) Support universal testing of all babies (79.5% versus 69.9%)
b) Not support testing in which women can opt out (52.2% versus 59.9%)
c) Not support women knowing how much alcohol or drugs make a test positive (48.9% versus 54.4%).

Women believed that a testing program would result in a decrease in the amount of drugs and alcohol used during pregnancy (66.2%), a decrease in the number of children born exposed to drugs and alcohol (63.7%), that babies would get the help they need early in life (95.0%), and that no one would feel discriminated against if everyone is tested (87.3%). In all cases, women who reported alcohol use were more likely to agree with the above statements.

Table 4.32. Women who strongly agreed or agreed to screening for their babies, types of information that women would need to know in order to agree to screening and the likely impact of routine screening based on alcohol self-report during pregnancy

	All Women	Alcohol use during pregnancy among drinkers		p-value
	n=1509* (%)	Yes (n=634)	No (n=792)	
		n (%)	n (%)	
Support universal screening in which women can refuse screening**	843 (57.7)	331 (52.2)	473 (59.7)	0.004
Support universal screening of all babies (no special consent) †	1002 (68.6)	504 (79.5)	551 (69.6)	<0.001
You would consent to the screening of your baby‡	1369 (93.8)	579 (91.3)	729 (92.0)	0.62
In order to consent you to screening you would need to know the following				
How much drugs or alcohol make a test positive	772 (52.3)	310 (48.9)	431 (54.4)	0.04
What happens with a positive test result	1431 (97.1)	610 (96.2)	756 (95.5)	0.48
Who has access to the information	1377 (93.4)	579 (91.3)	735 (92.8)	0.30
How effective medical care is for children who test positive	1435 (97.4)	604 (95.3)	766 (96.7)	0.16
The chance that a baby will have a problem if a test is positive	1444 (98.1)	608 (95.9)	772 (97.5)	0.09
If all babies were routinely tested then following may be the result				
Women will cut back on drug and alcohol use during pregnancy if their baby will be tested	972 (66.2)	440 (71.2)	493 (63.1)	0.001
There will be a decrease in the number of children born exposed to drugs and alcohol	934 (63.7)	418 (67.6)	477 (61.2)	0.012
Babies will get the help they need early in life	1392 (95.0)	598 (96.6)	733 (94.1)	0.03
If all women are tested no one will feel like they are being discriminated against	1280 (87.3)	552 (89.6)	666 (85.3)	0.02
Women will have babies at home to avoid drug and alcohol screening	403 (27.5)	164 (26.5)	218 (27.9)	0.59
Women will be less likely to seek prenatal care	652 (44.4)	275 (44.5)	344 (44.0)	0.87
Women will be less likely to trust their health care providers	484 (33.1)	201 (32.5)	258 (33.0)	0.84

*Actual number of respondents varied between 1424-1509.

**You would support universal screening of babies for drug and alcohol exposure in which women are allowed to refuse screening of their infant.

†You would support universal screening of all babies as part of routine care (i.e. women do not provide special consent).

‡If universal screening for drug and alcohol exposure was performed in Alberta you would consent to the screening of your baby.

4.3.4 Agreement with Scenarios Related to Screening

Almost all participants agreed (97.6%) that a woman should consent to screening if the consequence of a positive screen meant that the woman stayed with her infant and both received help (Table 4.33). With the same consequence, 81.3% of women felt that a doctor should be able to test without consent. With a consequence of a baby being placed in care while the mother receives help 80.5% of subjects felt that a woman should consent, 64.6% felt that a doctor should be allowed to test without consent and 27% felt that a woman should be able to refuse testing. Women who reported alcohol use were more likely to agree that the doctor should be able to test without consent for all scenarios except for staying together and not receiving help (data not shown).

Table 4.33. Frequency and percentage of women who strongly agreed or agreed with scenarios related to alcohol and drug screening of newborns in a cross-sectional survey examining factors related to willingness to consent

	Doctor should be able to test without consent [**]	**Jane should consent to screening[†]**
	N=1497[*] n (%)	**N=1497[*] n (%)**
Baby placed into care & Jane receives help[‡]	964 (64.6)	1191 (80.5)
Jane & baby stay together & receive help[§]	1213 (81.3)	1440 (97.6)
Jane & baby stay together but don't receive help[‖]	167 (11.2)	271 (18.4)
Jane & baby stay together but only Jane receives help[¶]	171 (11.5)	371 (25.2)

[*] N varied between 1475 and 1497.

[**]Dr. Smith should be able to test Jane's baby without asking for her consent if the consequence of a positive test may be that:

[†]Jane should consent to the screening of her baby if the consequence of a positive test may be that:

[‡]Her baby will be temporarily placed in care while Jane is assessed for drug and alcohol problems and receives help.

[§]Jane and her baby will stay together and they both receive the help that they need.

[‖]Jane and her baby stay together but neither receives any assessment or extra help.

[¶]Jane and her baby will stay together while only Jane receives the help that she needs. Jane's baby receives no extra help.

4.3.5 Predictors of Consent

Women who would not consent were more likely to be 30 years of age or older married, primipara, have at least a university degree and were less likely to report alcohol use during pregnancy (Table 4.34). The multivariate model revealed that women who would consent were more likely to be multiparous and to have lifestyle risk factors that put them at risk of an alcohol exposed pregnancy (Table 4.35).Those who would consent to screening believed that if women were informed they would take action to reduce consumption and the number of alcohol exposed pregnancies would be reduced. Although it did not reach significance, women who would have liked additional information about alcohol use were those with lifestyle risk factors and most likely to consent.

Women who would not consent were also less likely to agree that a testing program would lead to a decrease in alcohol and drug use during pregnancy (31.7% versus 68.5%) and decrease the number of children exposed to drugs and alcohol in utero (30.2% versus 65.8%). They were less likely to agree that women would not feel discriminated against (47.6% versus 89.5%), were less likely to support a universal testing program (14.3% versus 79.4%), and were more likely to agree that a woman would need to know much drugs or alcohol makes a test positive (68.3% versus 51.5%).

Table 4.34. Differences between women who would or would not consent to screening of their infant in a cross-sectional survey examining factors related to willingness to consent to drug and alcohol screening of infants

Group	Would consent (n=1369)	Would not consent (n=63)	p-value
	n (%)	n (%)	
Demographics			
≥ 30 years of age	726 (53.3)	43 (71.7)	0.005
Married	1075 (79.0)	56 (91.8)	0.01
Primipara	635 (46.8)	37 (60.7)	0.03
≥ University undergraduate degree	530 (38.9)	38 (62.3)	<0.001
≤ Graduated high school	355 (26.1)	4 (6.6)	<0.001
Lifestyle			
Smoked in 12 months prior to pregnancy	383 (28.1)	6 (9.8)	0.002
Smoked during pregnancy	186 (13.7)	3 (4.9)	0.05
Drank alcohol in 12 months prior to pregnancy	1090 (80.1)	42 (68.9)	0.03
Binge drinking in 12 months prior to pregnancy	558 (51.3)	15 (36.6)	0.007
Alcoholic drinks consumed in a typical week	1.63 (SD 3.79)	1.53 (SD 3.29)	0.87
Did not drink alcohol during pregnancy	790 (57.7)	38 (58.7)	0.90
T-ACE≥2	528 (38.6)	11 (17.5)	<0.001
Number of Risk Drinking Factors (Positive T-ACE, Alcohol Use in Pregnancy, Binge Episode)			
0	323 (23.6)	24 (38.1)	
1	536 (39.2)	26 (41.3)	0.008
2	401 (29.3)	13 (20.6)	
3	109 (8.0)	0 (0.0)	
Liquor	200 (18.3)	2 (4.8)	0.02
Opinions related to the result of routine screening			
Women will cut back on drug and alcohol use during pregnancy if their baby will be tested	938 (68.5)	20 (31.7)	<0.001
There will be a decrease in the number of children born exposed to drugs and alcohol	901 (65.8)	19 (30.2)	<0.001
Babies will get the help they need early in life	1305 (95.4)	56 (88.9)	<0.001
If all women are tested no one will feel like they are being discriminated against	1225 (89.5)	30 (47.6)	<0.001
You would support universal screening of all babies as part of routine care	1087 (79.4)	9 (14.3)	<0.001
In order to consent a woman would need to know			
How much drugs or alcohol make a test positive	705 (51.5)	43 (68.3)	0.03

Table 4.35. Adjusted odds ratios for characteristics of women who would consent versus those who would not consent to drug and alcohol screening of their newborn in a cross-sectional survey examining factors related to willingness to consent to drug and alcohol screening of infants

Characteristic	Would Consent (n=1369) n (%)	Would Not Consent (n=63) n (%)	AOR* (95% CI)
Demographics			
Multiparous	723 (53.2)	24 (39.3)	2.14 (1.20-3.80)
Lifestyle			
Smoked cigarettes prior to pregnancy	383 (28.1)	6 (9.8)	2.70 (1.09-6.73)
T-ACE Positive (≥2)	528 (38.6)	11 (17.5)	2.24 (1.11-4.51)
Binge drinking prior to pregnancy recognition	558 (40.8)	15 (23.8)	1.90 (0.99-3.60)
Information during pregnancy			
Would have liked additional information on alcohol use during pregnancy	101 (7.6)	1 (1.6)	6.02 (0.76-47.55)
Received information on prenatal alcohol use from partner	725 (53.3)	22 (36.1)	2.00 (1.11-3.59)
The likely outcome of a screening program is that:			
Women will cut back on drug & alcohol use	938 (68.6)	20 (31.8)	2.15 (1.07-4.31)
No one will feel like they are being discriminated against if all women are tested	1225 (89.5)	30 (48.4)	5.94 (3.34-10.57)
There will be a decrease in the number of children born exposed to drugs and alcohol	901 (65.9)	19 (30.2)	2.10 (1.06-4.18)

*AOR: Adjusted odds ratios are adjusted for all other characteristics in the table.

Chapter Five: Discussion

In this chapter, findings for each of the major study questions are discussed in separate sections.

5.1 Association between Maternal Self-Report of Alcohol and Drug Use and Biomarker in Meconium

The presence of FAEEs in meconium has been used to screen infants for prenatal alcohol exposure on a research basis given that maternal self-report underestimates exposure (86;100). Mac *et al* were the first to report FAEEs in meconium as a marker of maternal alcohol use during pregnancy (245). Fatty acid ethyl esters are produced by an enzymatic process involving esterification of alcohol with free fatty acids and begin to accumulate in meconium at approximately 20 weeks gestation. Fatty acid ethyl esters do not cross the placenta and are therefore thought to be an indication of fetal ethanol exposure (101). In addition, only select tissues including fetal heart and brain can metabolize alcohol to FAEEs leading some to conclude that FAEEs in meconium are a sign of fetal brain exposure to alcohol (101-103;243). Finally, FAEEs are cytotoxic and it is hypothesized that FAEEs may be involved in damage to the fetal brain associated with alcohol exposure (101-103;106;243).

This study revealed no evidence of association between maternal self-report of either abstinence or alcohol use and presence of FAEEs in meconium. Several cut-offs for FAEEs were examined including 50 ng/g, 500 ng/g, 10,000ng/g, any oleic acid and any linoleic acid based on cut-offs used previously in the literature. The lack of association between maternal self-reported alcohol use during pregnancy and concentration of FAEEs in meconium is consistent with the report of Derauf *et al* (247).

However, this finding is contrary to the work of Bearer *et al*, and Chan *et al*, who found an association between maternal self-report and FAEE concentration in meconium (92;93;107;108;235). At a minimum, Bearer *et al* found a sensitivity of 72 % and a specificity of 51 % in distinguishing the consumption of an average of one drink per week in the third trimester from abstainers (92;93;107). Most recently, in a study of 124 mother-infant dyads, Ostrea *et al* found that ethyl linoleate as a marker for prenatal alcohol exposure had a sensitivity of 26.9% but a specificity of 96.8% and positive predictive value of 96.2% (105). Given that the primary attribute of a screening test is sensitivity, the results of the study of Ostrea *et al* indicate that FAEE screening in meconium could not be considered a good candidate for identifying maternal alcohol use as part of a screening program.

Bearer *et al* found that two FAEEs, ethyl linoleate and ethyl oleate, were markers of self-reported alcohol use in the month prior to pregnancy and during pregnancy at maternal self-reported alcohol consumption as low as 1 drink per week (92;93;107). If alcohol consumption prior to pregnancy (at least one drink per week) was used as an indicator of elevated FAEEs, then the sensitivity was 68% and the specificity 48%. In a high risk group, ethyl oleate at a cut-off of 32 ng/g had a sensitivity of 84.2%, specificity of 83.3% and area under the receiver operator curve of 0.92 for women who consumed 1.5 average ounces of absolute alcohol per drinking day (94). Bearer *et al* used alcohol use prior to pregnancy as a proxy for alcohol use during pregnancy, given maternal under-reporting (92-94). Similar sensitivity and specificity values were found in the work of Chan *et al* using total FAEE concentration rather than a specific FAEE species (235). In other words, FAEEs in meconium in these studies helped identify women who had

already been identified by non-invasive interview techniques. One could argue that given the agreement between maternal report or researcher/clinician assigned ‘risk group’ and level of biomarker in these studies the use of a biomarker on a population basis is not indicated. Instead, the interview methods to ascertain maternal alcohol consumption or risk group used by Bearer *et al* and Chan *et al* could be adopted on a wider basis to identify maternal prenatal alcohol use in the clinical setting. In addition, in the context of a screening program for women in Calgary, FAEE in meconium should be sensitive and specific for identifying women who consume alcohol until pregnancy recognition. Given that this represents approximately 50% of the perinatal population FAEE would not be a clinically meaningful or useful tool in terms of identifying infants or discriminating those at risk.

The lack of a ‘gold standard’ for confirming prenatal alcohol use is a challenge for this area of research. Derauf *et al* questioned the practice of generating sensitivity and specificity information for FAEEs given the lack of a ‘gold standard’ measure (247). In addition, the rationale for conducting FAEE screening is that maternal report of prenatal alcohol use is flawed and inaccurate. Therefore, any assessment of the relationship between FAEE concentration and maternal report should demonstrate limited association at best. Derauf *et al* analyzed the data from their study of maternal self-report and level of FAEE in meconium for 411 infants in Hawaii and reanalyzed Bearer *et al*’s published data using a statistical measure of agreement, the Kappa coefficient. The rationale for using the Kappa coefficient was that given the inaccuracy of maternal self-report and the lack of a ‘gold standard’ for maternal alcohol use, a measure that describes agreement between two imperfect measurement methods is more appropriate (247). Derauf *et al*

found no agreement between self-reported third trimester ethanol intake and presence of FAEE in meconium. In addition, there was poor agreement between maternal self report and FAEE in their reanalysis of the data from Bearer *et al*. Similar to the population in the MEC Study, Derauf *et al*'s data were from a population-based sample with moderate self-report of alcohol use during pregnancy. Of note, Derauf *et al* found that there was an association between total FAEE concentration and lower 1 minute Apgar scores and between ethyl oleate and decreased birth weight (247). A similar trend was seen in the current study between FAEE concentration and 1 minute Apgar scores, but this did not reach statistical significance.

The current study used a maternity clinic population-based sample in which overall prevalence of alcohol use during pregnancy, amount of alcohol consumed per occasion and presence of FAEEs was moderate. Meconium positive for FAEEs of between 15 and 21% of samples depending on cut-off is consistent with the prevalence of meconium samples positive for FAEE above a cut off of approximately 2 nmol/g (approximately 500ng/g) reported in the literature (97;108;247). Given the similarity across several different populations with assumed different rates of alcohol use during pregnancy, this raises the question of what influences FAEE concentrations in meconium. In this study, the outcome of no association between maternal self-report and concentration of FAEE in meconium may be attributed, in part, to the improved randomness of the population-based sample as compared to the majority of previous studies, which have focused on marginalized and at-risk groups with histories of alcohol abuse or dependence.

A profile of women who had infants with the highest concentration of FAEEs in meconium in terms of lifestyle and demographic characteristics did not reveal characteristics consistent with prenatal alcohol use. Women who had children with meconium positive for FAEEs were less likely to skip breakfast; however the clinical interpretation of this and the potential impact on FAEE concentration is unclear. There was no association between known risk factors for alcohol use during pregnancy, such as smoking, low self esteem and history of abuse, and presence of FAEEs in meconium (72-74;178-181). History of abuse, depression, low self-esteem and psychological distress are risk factors for substance abuse during pregnancy (222;225;300). Tobacco use and drug use are correlated with alcohol use in general and during pregnancy, and one would expect a higher prevalence of tobacco and drug use in subjects with elevated FAEEs. If FAEE concentration was reflective of alcohol use, then one would expect to see a difference in psychosocial characteristics between those with high and low FAEE concentrations. Higher SES has also been identified as a risk factor for prenatal alcohol use and in this study 91.7% of the positive samples at a cut-off of 500 ng/g were collected at Foothills Medical Centre versus 71.7% of the negative samples. This is consistent with the demographic, lifestyle and ethnic characteristics in northwest Calgary, which tends to be higher socioeconomic status (SES) versus the northeast with lower SES and non-Caucasian ethnicity.

This is the first study to report an association between male gender and prevalence of FAEEs in meconium. Male infants represent 49% of the sample but 66.7% of the positive FAEE samples. Soderberg *et al* report that FAEE serum concentrations in men are 2-fold greater than those found in women when given a controlled, weight-

adjusted ethanol dose (244). Of note, the sex ratio (male:female) reported for FASD in the literature varies by study but does not shown a specific predilection for disease in one sex (204;211;301). Little *et al* found that one drink per day in the week prior to pregnancy recognition was associated with a decrease in birth weight of 225 g for male but not female infants, suggesting that fetal susceptibility to alcohol my vary by sex (211). Chan *et al* found no statistical difference by gender for the prevalence of positive samples in their study of abstainers in Jerusalem and women in Toronto (235). The underlying physiologic mechanism for gender differences in FAEE concentrations in serum and in meconium has not been determined.

The lack of self-reported alcohol use among women with FAEE concentration above 10,000 ng/g is an important observation in this prospective study because it is contrary to the causal relationship implied by early case reports (95). Indeed, 2 of the samples in this study had FAEE concentrations above 100,000 ng/g, which approaches the highest value previously reported in the literature. Both of these women reported alcohol abstinence. However, a finding of elevated FAEEs in women who deny alcohol use as well as the absence of FAEEs amongst women who report alcohol use has been noted by others (92-94;107;108;232;234;247). The absence of FAEEs in the meconium of infants whose mothers reported alcohol use, in some at levels averaging greater than 5 drinks per week, indicates the importance of understanding the impact of ethnicity, diet, genetic polymorphisms in alcohol dehydrogenase and acetaldehyde dehydrogenase, endogenous alcohol production, type of alcohol use, and co-morbid conditions on presence of FAEE. Most recently in a series of *in vitro* experiments with human platelets and red blood cells, platelets were demonstrated to incorporate and synthesize FAEEs

from ethanol with subsequent production of potentially toxic free fatty acids and ethanol upon hydrolysis (302;303). Some biological conditions (e.g., diabetes, short bowel syndrome) can lead to endogenous alcohol production in the intestine (304-307). If this occurred in a pregnant woman it could lead to very low concentrations of alcohol in the blood that could cross the placenta to the fetus and result in FAEEs in meconium. However, this is unlikely as the levels of alcohol produced are $1/10^{th}$ to $1/100^{th}$ that obtained with one alcoholic drink unless there is extremely rare underlying pathology. The MEC Study results and the antecedent literature highlight the need to understand the biological characteristics, including genetic polymorphisms of enzymes involved in alcohol and fatty acid metabolism, of women and infants with elevated FAEE concentrations in meconium.

Too few of the meconium samples had detectable levels of biomarkers for drugs of abuse to comment on secondary research questions related to drug metabolites in meconium. However, 9% of women reported street drug use (predominantly cannabis) prior to pregnancy with only 3% of women continuing to use street drugs during pregnancy. These rates are consistent with rates from Canadian and American studies (219). Women who engage in binge drinking during pregnancy are more likely to smoke cigarettes, use various illicit substances (e.g. stimulants, cannabis, opiates, hallucinogens, and inhalant) and be young and single. These maternal characteristics and the genetic susceptibility of the child also affect the likelihood and severity of disabilities in the child (308). In Canada, cannabis is the most widely used illegal drug. The highest rate of drug use is amongst women 15-24 years of age with the prevalence ranging from 25% at age 15 to 19% at age 24 (221). In the National Institute on Drug Abuse 1988 survey 8.8% of

women of childbearing age reported using drugs in the month preceding delivery and 30% of women 18 to 34 reported use of an illegal drug in the preceding year (219). Given that tobacco use and street drug use during pregnancy are risk factors for alcohol use during pregnancy, one would expect a higher prevalence of tobacco and drug use in subjects with elevated FAEE concentrations, however, our data revealed no such association (225).

While there was no association between maternal self-reported alcohol use, T-ACE score, known risk factors for alcohol use during pregnancy and presence of FAEEs in meconium, the T-ACE screen seemed to identify women with other documented risk factors for alcohol use, which was consistent with the work of McNamara *et al* (87;309). The T-ACE scores were positive for half of those who reported alcohol use in this study, which is consistent with the proportion who report binge drinking episodes. The T-ACE identified women with a history of binge drinking, a history of alcohol problems, and history of current alcohol use as well as associated risk factors including a history of abuse and street drug use. T-ACE is thought to be more effective than medical record review and informal clinician questions in identifying women at risk for prenatal alcohol use (87;91;309). Chasnoff notes that an informal interview with a mother inquiring about alcohol and drug exposure results in under-reporting, whereas a more formal and organized interview increases reporting five-fold (82). The T-ACE may identify women with psychosocial factors associated with prenatal alcohol use who readily disclose information related their pre and perinatal substance use pattern. Women who have a risk drinking pattern of alcohol use who are not captured by the T-ACE (false negatives) may be a group that is less trusting of health care providers, less likely to disclose any

information regarding there substance use and also be more likely to answer all screening questions, like those on the T-ACE, in the negative. As evidenced in this study, women who self-reported risk drinking prior to and during pregnancy were identified by T-ACE but not by FAEEs in meconium. Women identified by T-ACE or self-report in prenatal or preconceptional visits may benefit from brief intervention and referral for services as recommended in the Alberta Clinical Practice Guidelines and for which there is some evidence base of effectiveness (23-25;310-313).

The rationale often cited for research in the area of FAEEs in meconium is as a test or screen to identify children at risk for developmental delay or a diagnosis of an FASD associated with prenatal alcohol exposure. Screening programs ideally identify asymptomatic individuals potentially at risk for a disorder or with a deficit (high sensitivity) who might then go on for more rigorous assessment and diagnosis as warranted. Studies in the area of FAEE testing in meconium to date have focussed on identifying the association between maternal self-report and level of biomarker. Given the rationale that maternal report is not a valid method of assessing exposure, there should be no association between maternal report and biomarker other than in the case of reported alcohol use in the last half of pregnancy. If testing for FAEE in meconium is to be considered for part of a screening program then the truly important association is that between level of FAEE and presence of deficit or developmental delay. The comparison between maternal report and level of biomarker is akin to comparing breast self-exam to mammography rather than comparing self-exam to the true outcome of interest which is breast cancer. The question that must be answered related to FAEE in meconium is whether or not the biomarker level or its presence identifies children at increased risk of

deficits associated with prenatal alcohol exposure. For this reason the children from the MEC study were followed up and assessed at 2 years of age to determine if there was an association between FAEE concentration and child development.

5.1.1 Generalizability, Strengths and Limitations

The study protocol closely followed the Standards for Reporting of Diagnostic Accuracy (STARD) criteria for evaluation of diagnostic tests. The STARD criteria were developed to ensure that studies collect and present adequate information for readers to fully understand the experiment and outcome. However, given that there is no 'gold standard' for alcohol exposure, in this study these criteria are used to maximize the quality of reporting of results rather than imply to that FAEE analysis is a diagnostic test. This study could be considered an assessment of diagnostic accuracy given that the STARD criteria were closely followed. Using those criteria we have demonstrated that the meconium FAEE test is not diagnostic of self-reported maternal alcohol use (285;286)

The study was based at low-risk maternity clinics which provide a high proportion of the prenatal care in the region. Eligibility criteria were broad and did not exclude subjects, thus the sample was similar to women in the Calgary Health Region in terms of age and parity. Study enrolment and retention rates were high for a community-based study, indicating that these results may be generalized to other urban maternity populations being served by a family physician. A sample collection rate of 70% is consistent with rates found in anonymous studies of prevalence of drug metabolites in meconium (99). The participants in this study were select in that they were seeking

prenatal care and agreed to participate in a study examining substance use during pregnancy. It is reasonable to assume that the group of participants would be less likely to use alcohol or drugs during pregnancy than mothers who did not seek prenatal care or agree to take part in the study. However, study participants reported periconceptional and prenatal alcohol and drug use in keeping with Canadian and American perinatal rates indicating that this is a representative sample of the population (229). Women who had some risk factors for substance use during pregnancy, e.g., history of suicidal thoughts or suicide attempts and being unemployed when wanting to work, were less likely to collect a sample after agreeing to participate, perhaps due to concerns related to substance use and fear of being identified. This is also consistent with a more marginalized group that is less likely to remain engaged with research.

In the literature there is an increased risk of miscarriage, preterm delivery and neonatal complications at elevated levels of alcohol use (225;314). Subjects with an elevated level of alcohol use that were enrolled may have been less likely to collect a sample, and such complications and birth outcomes would not have been reflected in this data. In addition, women who drink heavily during pregnancy are less likely to have an adequate diet (225). However, these same women may be less likely to seek prenatal care and therefore were unlikely to have been recruited for this study at a maternity clinic. Women were enrolled in the study late in pregnancy so those women who may have consumed alcohol and given birth preterm were not included. Given the association between prenatal alcohol use and preterm birth it would be important in future studies to try to capture these women (208).

Studies that utilize self-report as a measure of alcohol consumption are vulnerable to information bias; specifically, differential misclassification and clinician expectancy bias. Information bias could result if those at greatest risk for alcohol consumption do not seek prenatal care, therefore providing no history or prenatal record for documentation of self-reported alcohol consumption at the time of birth. Clinician expectancy bias results when a clinician more rigorously interviews an individual from a group perceived at risk (e.g., Aboriginal) for alcohol and drug exposures than an individual from a group perceived to be at lower risk. In this study ascertainment of alcohol use and risk of alcohol use was by several different standardized and validated methods and subjects were interviewed in a non-threatening manner by trained research assistants and clinicians. This strategy was aimed at minimizing information bias. Despite the study team's efforts self-report of alcohol use will often be inaccurate given societal values related to alcohol use during pregnancy. However, in some cases women evidently felt comfortable volunteering relatively high levels of prenatal alcohol use.

Strengths of the study that contribute to the validity and generalizability of the results include: a data set that was complete for most of the infants, with an abundance of data collected at several points in time; a relatively representative sample from a low risk maternity clinic; a large sample size that allowed for relatively accurate estimates of descriptive variables; active data verification which reduced data errors; missing data and missing cases were not an issue as extensive baseline information was collected prior to subject enrolment and sample collection; and all subjects provided data out to 10 weeks postpartum.

5.2 Biomarker in Meconium and Child Development

Currently there is a paucity of research pertaining to biological markers, or other screening tools, that identify infants at risk for health and developmental problems associated with maternal prenatal alcohol use. This is the first study to report an association between a biomarker, FAEEs in meconium, and child motor development. Specifically, children in this study were found to be delayed on the BSID-II Psychomotor Development Index (PDI), which is an overall measure of gross and fine motor skills including degree of body control, coordination of the body and large muscles, finer motor skills of the hands and fingers, dynamic movement and postural stability (289). The level of FAEE was correlated with the BSID-II PDI, and in bivariate analysis and linear regression analysis a difference of between 7-9 points on the PDI was seen between FAEE positive and negative groups. There were also differences when children were categorized as delayed on the BSID-II PDI with 50.0% of children with elevated levels of FAEE categorized as delayed versus 17.2% of unexposed children. In logistic regression analysis an OR of 39.4 was found after adjustment for infant sex, birth weight, report of daily alcohol use prior to pregnancy recognition and maternal age greater than 35 years at delivery, indicating for children with a FAEE concentration ≥ 10,000 ng/g the odds of having motor delay was approximately 40 times that of children with FAEE < LOD. Children with FAEE ≥ 5,000 ng/g were 27 times more likely to have motor delay than children with FAEE < 5,000 ng/g. Significant odd ratios were found for all examined dichotomous FAEE cut offs with the adjusted odds ratios increasing in magnitude from FAEE ≥ LOD to FAEE ≥ 10,000 ng/g. Children with elevated FAEEs in meconium also were older in rolling from back to front and tended to have an approximate one month

delay for the motor milestones of crawling, pulling to sitting, and walking unassisted when compared to children who had been negative for FAEEs. The results from this study suggest that all concentrations of FAEE greater than the LOD are associated with an increased risk of motor delay with greatest risk seen in children with FAEE ≥ 5,000 ng/g.

A motor deficit was also seen in children whose mothers reported daily alcohol use prior to pregnancy recognition. None of these children had meconium positive for FAEE. Prenatal alcohol exposure by maternal report was examined by trimester of exposure, frequency of binge episodes, drinks per week, drinks per occasion, and number of drinking occasions per month. The only difference between infants with and without motor delay was maternal report of daily alcohol use prior to pregnancy recognition. Maternal report of alcohol use during pregnancy was only associated with delay at 2 years of age for 4 children, confirming that maternal report alone cannot accurately identify all children at risk of delay.

The motor delays seen with the children in this study who had elevated FAEE concentrations are consistent with reports in the literature of children who had ‘low’ dose prenatal alcohol exposure who do not meet the diagnostic criteria for an FASD (165). The difference in motor delay between those with elevated FAEE and those without represents half a standard deviation on the BSID-II and is not consistent with a profound deficit like a Motor Skills Disorder, but may represent a clinically important difference. In the Ottawa Prenatal Prospective Study, a cohort of high to middle socioeconomic status mothers similar to the cohort in the MEC Study, Gusella and Fried found that a relatively low level (less than one drink per day averaged across pregnancy) of alcohol

exposure was significantly associated with psychomotor deficits as assessed by the BSID at 48 months but not 12 and 24 months (133). Kalberg *et al* assessed the motor functioning of 14 children with FAS between 2 and 5 years of age using the Vineland Adaptive Behavior Scales and compared them to children with no alcohol exposure and children with prenatal alcohol exposure but no diagnosis of an FASD (315). Children with FAS showed delays on the overall Motor Score and children with prenatal alcohol exposure were also noted to have motor deficits. The authors suggest that there is a continuum of neurobehavioral deficit in fine motor and overall motor skills in children, ranging from 'mild' deficits seen in those with prenatal alcohol exposure to more severe deficits in children with FAS (315). Given the association between alcohol exposure and motor deficits as an early sign of overall psychomotor dysfunction there is growing recognition of the importance of assessing early motor function of children with potential prenatal alcohol exposure.

Kaplan-Estrin *et al* evaluated 92 African American children at 13 and 26 months using the BSID (316). After controlling for confounders they found that prenatal alcohol exposure was associated with a deficit on the MDI and a tendency to deficit on the PDI that did not reach statistical significance at 13 months (316). At 26 months an association between prenatal alcohol exposure and a deficit on the PDI persisted and was statistically significant, particularly in the domains of fine motor and spatial learning (316). Roebuck *et al* found that children who were exposed to alcohol prenatally had delayed motor development in both fine and gross motor skills and demonstrated a prolonged latency period in reflexes indicating that the motor deficit may in part be due to CNS damage (317). Connor *et al* assessed balance and coordination of adults diagnosed with an FASD,

unexposed controls and those exposed prenatally to alcohol but without an FASD diagnosis (318). Children with an FASD and those exposed prenatally to alcohol had motor deficits in both fine and gross motor domains when compared to unexposed controls (318). The differences between FAEE positive and negative groups in the MEC study are consistent with delays and deficits seen in children with a history of prenatal alcohol exposure in the literature, perhaps providing evidence that FAEE in meconium may reflect prenatal alcohol exposure in the absence of maternal report.

There is one previous study that examined the association between level of a biomarker for alcohol use (FAEEs) or drug use in combination with self reported alcohol use and developmental mental outcomes for infants (195). Noland *et al* found that alcohol-exposed children, as determined by maternal report and FAEE status, had lower birth weights and birth lengths, smaller head circumferences and worse tapping-inhibition performance, a measure of executive functioning, at four years of age (195). There were no differences in motor skills development. The study by Noland *et al* was conducted with a group of children of extremely low socio-economic status birth mothers from the inner-city in Detroit who had low IQs (mean 74.6) (195). By comparison, the mean IQ of mothers in the MEC Follow Up Study was 113, approximately 40 points higher than the women in the Nolund *et al* study. The group studied by Nolund *et al* is not comparable to the well educated, middle socio-economic status women under a universal health care system, like the women who participated in the MEC Study. However, it will be important to see if the difference that was seen on assessment of executive function, something that cannot be done with 2 year old children given their developmental stage, can be seen with the children in the MEC Follow Up Study as they age.

There was no evidence of differences between FAEE groups on the BSID-II Mental Development Index. Children with a diagnosis of an FASD may have signs of cognitive deficit at a young age, but these differences are not as evident in children with prenatal alcohol exposure who do not have a diagnosis of an FASD (160). Streissguth *et al* found that children not diagnosed with FAS or FAE who were exposed to 1 to 2 drinks per day averaged across pregnancy had an IQ that was 7 points lower than a non-exposed comparison group at age 7 (160). There is a range in deficits in the literature associated with 'light' to 'moderate' alcohol use (1-2 drinks per day) during pregnancy from 7 to 24 IQ or MDI points. Bailey *et al* found that a binge pattern of prenatal alcohol use in a sample of over 500 black 7-year old children was associated with an increased risk of mental retardation (i.e., IQ <70) and delinquent behavior (319). In the Ottawa Prenatal Prospective Study Gusella and Fried found that relatively 'low' levels (less than one drink per day averaged across pregnancy) of alcohol exposure in a cohort of high to middle socioeconomic status mothers were significantly associated with poorer mental development, as determined by BSID (165). At 2 years, the association was still significant, but by 36 and 48 months low levels of alcohol exposure were no longer associated with poorer mental development (131;133;134). No difference was seen between the children in this study based on FAEE concentration. It may be important to see if differences in cognitive ability become apparent as the children in this study reach school entry, which is when the majority of the children in the literature were assessed.

There was also no evidence of differences between FAEE groups in the areas of behavior, adaptive behavior and temperament. There was a tendency that did not reach statistical significance for FAEE positive subjects to have lower scores on the ABAS

Conceptual Composite and Practical Composite domains. This tendency was also seen when subjects were categorized as 'Below Average' by standardized score on the ABAS. There was also no evidence of differences between groups on more generalized developmental screening tests like the Ages and Stages Questionnaire and Nippissing District Developmental Screener, indicating that the differences between groups in the MEC Study required more standardized objective assessment, like the BSID-II, to be detected. In addition, the ages at which differences in behavior and temperament have been reported in the literature tend to be in children at school entry. Sood *et al* found in a study of 501 black children at 6 to 7 years of age that those whose mothers reported prenatal alcohol use had higher CBCL scores (indicating more dysfunction) in the domains of aggressive, delinquent, anxious/depressive and withdrawn behaviors (172). Differences in behavior and temperament between FAEE groups were not identified in this study at 2 years of age. This is consistent with the literature, where no differences were found in behavior early in childhood. Behavioral problems become more prominent as children with prenatal alcohol exposure age(5).

Children with FAEE concentrations above the limit of detection were more likely to have Apgar scores < 7 at 1 minute and tended to have lower birth weights and lower birth lengths. As the children aged they were approximately 600 grams lighter at 12 months and tended to be lighter at all time points, although this did not reach statistical significance. In the Maternal Health Practices and Child Development Project, a longitudinal study of the long-term effects of prenatal alcohol exposure, a dose-dependant linear relationship was observed between prenatal alcohol exposure and growth deficit of height, weight, and head circumference (129;130). Drinkers were defined as having 3 or

more drinks per week in the first trimester, while non-drinkers drank less often (129;130). Both disadvantaged and advantaged populations showed an association between fetal alcohol exposure and growth (1;65;131-136). In guinea pigs there is an inverse relationship between birth weight and level of FAEE (320). The results reported in the MEC Study are consistent with deficits in weight and growth associated with prenatal alcohol use as determined by maternal report in human studies and by FAEE level in animal studies.

Protective factors for motor development in this study were female sex and higher household income, while protective factors for mental development included higher maternal IQ, higher household income and female sex. The protective effects of maternal IQ, SES and female sex on child development are well documented in the literature (1;129;130;133;134;164;168;172;192;194;195;211). It is possible in the MEC study that cognitive development as determined by MDI is protected more so than the psychomotor development (PDI) due to the relatively high maternal IQ of participants, which was more strongly correlated with child MDI. Additionally, there has been a trend in Canadian society to foster and encourage early child cognitive development. Parents are encouraged to read and talk to their children and introduce them to structured educational playgroups and preschool at a young age. At the same time, not as much emphasis is placed on early physical activity and physiotherapy related activities. Male sex was associated with an increased prevalence of meconium with FAEE above the LOD and a tendency to have a higher concentration of FAEEs in meconium. In the literature there is no difference in the sex ratio for FASD. However, Little *et al* found that one drink per day in the week prior to pregnancy recognition was associated with a decrease in birth

weight of 225 g for male but not female infants, suggesting that fetal susceptibility to alcohol may vary by sex (211). Differences between how male and female fetuses metabolize ethanol and produce FAEE need to be understood if FAEE in meconium are to be used to screen for infants at risk for delay.

While high SES was protective for cognitive development a family income ≥ $90,000 also tended to be associated with an elevated FAEE in meconium. Women with high SES also tended to be older than 35 years of age. Maternal age has been described as a risk factor for deficits associated with prenatal alcohol exposure in studies in which the association between fetal alcohol exposure and growth deficits only holds for women over 30 years of age (138;139). The authors concluded that postnatal and maternal characteristics contribute to observed effect (138;139). It is unclear if maternal age is related to an established pattern of alcohol use, other behavior, or physiologic changes related to aging. Increasing maternal age may identify women with higher SES, a higher level of education and a greater degree of autonomy in their personal and professional lives. These same women may be protective of their personal lives and less willing to tolerate interference in their affairs, including discussions related to risk behaviors and prenatal drug and alcohol use with their care-providers. It is important to explore methods of engaging these women with a goal of optimizing prenatal care.

Factors that have been identified in the literature as playing a role in child development were examined in this study. There was no evidence of association between mental or motor delay and home environment, ethnicity, education, maternal drug use, breastfeeding, temperament, smoking, parenting satisfaction, and nurturance. This may be related to the overall homogeneity of the sample in terms of SES, education, ethnicity,

and parenting satisfaction. Perhaps differences would have been seen if the study had also captured women from a more marginalized group or different cultures.

Of interest, report of alcohol use during pregnancy was greatest at 2 years postpartum on a self-administered form, with 44.8% of women reporting some alcohol use (including prior to pregnancy recognition) versus 35% when assessed during pregnancy or 10 weeks postpartum. This is consistent with a study by Jacobson *et al* in which maternal report of prenatal alcohol use was higher at 13 months post-partum than at any point during pregnancy or immediately post-partum (321). In addition, they found that the report of alcohol use at 13 months was associated with the neurobehavioral deficits that they were seeing in the children in the study, while report of alcohol use at any other point in pregnancy was not. Adverse effects were evident with self-reported doses of one drink per day averaged across pregnancy (321). In the MEC Study, there was no association between FAEE and postpartum report and no difference between children based on report of prenatal alcohol use at two years post-partum. In addition, a greater proportion of subjects in the FAEE negative group reported frequent alcohol use prior to pregnancy recognition, greater than two drinks per sitting prior to pregnancy recognition, T-ACE positive, binge episodes prior to pregnancy recognition, alcohol use in the third trimester, and 1-5 drinks per week during pregnancy. Maternal report of alcohol use and FAEE concentration in meconium would appear to capture different types of alcohol use, if FAEE in meconium is indeed evidence of prenatal alcohol use.

It is important to note that differences were not appreciated between children on a 30 to 45 minute paediatrician visit, other than differences on developmental milestones, and differences in weight at 12 months. There were no differences in dysmorphic

features, or in parental or paediatrician concerns about gross motor, fine motor or developmental delay. In addition, there were no differences in the mother's or father's history of mental health or behavior problems. The children in this study who had motor delay did not have a deficit that was readily apparent to parents or physician. None of the children had features that resulted in referral for assessment regarding a potential diagnosis of an FASD. This highlights the need for a high index of suspicion and involvement of a multidisciplinary team including pediatricians, psychologists, social workers, physiotherapists and speech language pathologists if children are going to be assessed and identified as requiring early intervention for a delay or deficit potentially associated with prenatal alcohol exposure.

This study demonstrated a difference in motor delay at 2 years of age based on FAEE group, which is consistent with the antecedent literature in human and animal studies for prenatal alcohol exposure. However, it is unclear that the children with elevated FAEEs were in fact exposed to alcohol prenatally, or if some other biological process which results in the production of FAEEs may have taken place. A consistent high level of alcohol use is not required for CNS damage. Olney *et al* demonstrated in rat and mouse models that massive neurodegeneration or neuronal apoptosis occurs during synaptogenesis, which occurs in the last trimester and first years of life in humans, following a single exposure to alcohol at a level that can be achieved with a binge episode or even with the consumption of only 1-2 drinks on a single occasion (144;145;322). This may be consistent with a single exposure in the last half of pregnancy that could potentially result in a positive FAEE test. Given the lack of or decreased liver function in the fetus, alcohol would circulate for a longer period of time

and more alcohol would be metabolized to FAEE than in an adult with a fully functional liver. In addition, one exposure to alcohol may result in FAEE production in the heart and brain of the fetus, resulting in damage to these organs as well as the presence of FAEE in meconium (101-103;106;243). FAEE in meconium may be evidence of a single prenatal exposure to alcohol that could have resulted in CNS damage and the psychomotor deficits that were detected in this study.

Olney *et al* demonstrated that a single exposure to alcohol resulting in levels as low as 50 mg/dL of blood ethanol in infant mice and rats, or the equivalent of a 0.05% blood alcohol level maintained for 30 to 45 minutes, results in the loss of 20,000 neurons throughout the CNS including the brain, spinal cord and retina (144;145;322). There is a dose response, with a single exposure at the equivalent of a binge level (5 or more drinks in one sitting) resulting in massive neuronal apoptosis (millions of neurons) on a more widespread basis. This level of exposure resulted in spatial learning and memory deficits at 1 month of age in pups (144;145;322). These authors also found that recovery from the deficit was associated with neuronal reorganization rather than neurogenesis (144;145;322). They concluded that neuronal apoptosis may be a key mechanism for FASD-related deficits, and that this neuronal reorganization may be evidence that recovery is possible for children with prenatal alcohol exposure.

The rationale often cited for research in the area of FAEEs is that they can be used as a test or screen to identify children at risk for developmental delay associated with prenatal alcohol exposure. Screening programs ideally identify asymptomatic individuals potentially at risk for a disorder or with a deficit (high sensitivity) who might then go on for more rigorous assessment and diagnosis as warranted. If testing for FAEEs in

meconium is to be considered for part of a screening program then FAEEs in meconium should identify or predict the presence of a deficit or developmental delay. As such, the diagnostic test parameters for FAEEs in meconium in combination with maternal reported alcohol use to identify individuals with a deficit or delay were generated and should be considered in evaluating how FAEE can be used as a tool within a screening program. At best, a sensitivity of 53.6% was obtained, indicating the probability of testing positive for FAEE given that there was delay was only 53.6%. Ideally, sensitivity should approach 100% with a screening test, ensuring that all individuals potentially at risk for delay are identified. However, not all developmental delay or motor delay would be due to one cause like prenatal alcohol exposure, given that mental and motor development are multifactorial. It would therefore be unrealistic to expect a screening test potentially indicative of prenatal alcohol exposure to identify all children with delay, i.e., high sensitivity. With a specificity of 98% the probability of having a negative test given that a patient has no delay is close to 100%. This high specificity is consistent with the finding of Ostrea *et al* for the association between maternal report of prenatal alcohol use and FAEE concentration in meconium (105). Therefore FAEE may be helpful in ruling out potential delay due to prenatal alcohol exposure, but would be no better than chance for identifying those with delay due to any cause. An area under the ROC of 0.63 was obtained for concentration of FAEE and its relationship to BSID-II PDI. This information reinforces that FAEE screening is inadequate as a stand alone method to identify all children at risk of delay. Again, this needs to be interpreted in the context of developmental delay being due to many different causes.

Given the evidence that children with prenatal alcohol exposure can have motor delay, maladaptive behavior, differences in temperament and lower IQ it may be important for children with elevated concentrations of FAEE in meconium or maternal report of alcohol use during pregnancy to have complete developmental assessments including fine and gross motor skills and assessment for diagnostic criteria for an FASD (35). Interventions could then be tailored to the specific deficit. At this point there is limited evidence for the types of intervention that may be beneficial for children that have been identified at a young age as having deficits associated with prenatal alcohol exposure, whether or not they meet diagnostic criteria for an FASD. The types of interventions that might be considered include those that have been examined with animal models by Christie *et al* (323-326). They demonstrated in a rat model that the introduction of early postnatal voluntary exercise can decrease or even eliminate deficits in spatial learning and in the equivalent of human learning and memory processing following prenatal alcohol exposure. They also demonstrated that postnatal exercise increased neurogenesis in the brains, in particular in the hippocampus, of both control and alcohol-exposed rats. Others have suggested, based on animal models, that children with an FASD may benefit from early motor training and therapy with improvement in not only fine and gross motor skills but also in behavior and overall function (327).

If the delays seen with the children in this study were truly associated with prenatal alcohol exposure then the prevalence of deficit associated with prenatal alcohol exposure not meeting diagnostic criteria for an FASD may be higher than previously thought. The implication of this work is that prenatal alcohol use is a much larger and more important public health problem than previously recognized, making early

identification and intervention to promote the neuronal reorganization proposed by Olney *et al* even more important. It will be important to follow the children in the MEC Study group to determine if the deficits seen at 2 years of age are stable, if they disappear with time or if they manifest as cognitive or behavioral deficits as the children age. In particular it will be important to study these children around the time of school entry, as a child with a relatively 'low' level of exposure at this age can present with hyperactivity, impulsivity, poor cooperation, poor eye-hand coordination, poor balance, poor tandem gait, central auditory dysfunction, cognitive defects, and delayed language (9;80;131;165).

5.2.1 Generalizability, Strengths and Limitations

The MEC Study was based at low-risk maternity clinics, which provide a high proportion of the prenatal care in the region. Eligibility criteria were broad and did not exclude subjects, and the sample was similar to women in the Calgary Health Region in terms of age and parity. Those who took part were similar to all women giving birth in this health region in terms of age, income, marital status, ethnicity, parity, and education (299). Mean maternal age was 30 years old at delivery, with the majority of births occurring to women aged 25 to 34. Study enrollment and retention rates were high for a community-based study, indicating that these results may be generalized to other urban maternity populations being served by a family physician in a population of relatively high SES, well educated women.

The calculated sample size for this study was achieved with 32 subjects with elevated FAEE concentrations and 100 subjects with FAEE concentration below the

LOD followed up at 2 years of age. A key requirement for this study was that an adequate number of subjects were followed up. The standard in the literature is a minimum of 70% of enrolled subjects followed up. Lower numbers threaten the validity of the study, as those who are lost to follow-up may be different than those who are not followed up. In this study we achieved a high participation and follow up rate among eligible subjects of 80.0%, which should not threaten the validity of the results. There was no evidence of difference in participation by FAEE status; however, there was a tendency towards a higher proportion of positive FAEE results in the participant group. Compared to women who participated in the study, women who did not participate or were lost to follow up were more likely to be of non-Caucasian ethnicity, have a lower degree of education, a lower household income, were more likely to report daily smoking, exercise less frequently, report a family history of alcohol problems, and report a history of suicide attempts. This is consistent with a more marginalized group that is less likely to remain engaged with research. However, subjects with elevated FAEE were not lost to follow up and there was no evidence of differential loss to follow up by FAEE status indicating that selection bias was not an issue in this study. Further research is needed to understand how to recruit and retain women from marginalized groups in research and program delivery.

Strengths of the study that contribute to the validity and generalizability of the results include: a data set that was complete for most of the infants, with an abundance of data collected at several points in time, including child hospital records; a representative sample from a low risk maternity clinic; a large sample size that allowed for accurate estimates of descriptive variables; active data verification which reduced data errors; and missing data and missing cases were not an issue as extensive baseline information was

collected. Multiple methods were used to capture lifestyle during pregnancy. This was important as there is some evidence that the prevalence of reported alcohol use increases when women are asked at several points in time using several strategies. In any study that is examining child motor and cognitive development it is crucial to control for maternal IQ in analyses, and that was done in this study.

An additional strength of the study at the time of follow up was that the primary outcome of the study was determined by standardized assessment with a psychologist who was blind to the exposure status of the infants. All participants and staff members were blind to the FAEE status of participants. Exposure information and outcomes were kept in separate databases and not merged until follow up was complete. Given that all study participants, enrollers, project coordinators and psychologists, were blind to exposure status there was a decreased likelihood that information and selection bias had an impact on the study results.

There are several potential limitations in this study that need to be considered. Studies that utilize self-report as a measure of alcohol consumption are vulnerable to information bias. To minimize information bias in this study, ascertainment of alcohol use and risk of alcohol use was assessed by several different standardized and validated methods, and subjects were interviewed in a non-threatening manner by trained research assistants and clinicians. Despite the study team's efforts self-report of alcohol use will most likely always be inaccurate given societal values related to alcohol use during pregnancy. However, women evidently felt comfortable volunteering a relatively 'high' level of alcohol use in some cases.

5.3 Maternal Willingness to Consent to Drug and Alcohol Screening of their Newborn

In this cross-sectional survey the majority of women (93.8%) who responded would consent to the screening of their own infant and approximately 70% would support universal screening as part of routine care. Women were more in favor of a program in which all women were tested. In focus groups, women told us that if women could opt out then those most at risk would opt out. Almost all women surveyed (97.6%) indicated that a woman should consent to screening if a positive test resulted in both the mother and infant receiving effective help. This level of acceptance is consistent with the high level of participation in prenatal HIV screening programs and newborn metabolic screening, which achieve participation rates approaching 100% using universal opt-out methods (264). These programs have effective newborn treatments (e.g., HIV infection, phenylketonuria) and, in the case of HIV, over time there has been a decrease in the stigma associated with identification of at risk infants, a dramatic increase in the effectiveness of treatment, and an increase in the acceptance of testing (328). Most recently, the Centers for Disease Control and Prevention, given the effectiveness of current antiretroviral treatment, called for routine universal and frequent screening for HIV of all patients, including pregnant women, using opt-out methods with no separate consent required (329).

The high level of support for alcohol and drug screening may be related to the perceived benefit of screening and early detection for the mother and child. The perceived benefit of the interventions associated with screening accounted for approximately 70% of the agreement with screening as seen by the difference in

proportion of women who would agree with screening with effective intervention (e.g., ‘receive help’) versus no intervention (e.g., ‘don’t receive help’) as a consequence of a positive screen. There is some evidence for the effectiveness of brief prenatal interventions to decrease or eliminate alcohol use during pregnancy, however, without regular follow up and reinforcement long term reduction may not be achieved (311;313;330). Participants indicated that evidence of effective care for those who screen positive at birth would be important. Early diagnosis could allow for earlier access to resources, additional educational funding, and improved parental understanding of their child’s behavior. This leads to better outcomes for children and a reduced likelihood of secondary disabilities (5;6;47;331) . However, there is no evidence to indicate that infant screening specifically identifies those most at risk of disability.

A majority of women indicated that they would need information about substance use, screening, how the screening results would be used and what the implications of a positive screen were at their first prenatal visit. Although participants were reluctant to indicate a need for additional information about substance use and pregnancy, the majority believed that women were unaware of the potential problems associated with fetal exposure to alcohol. This paradox is difficult to explain but may suggest that strategies to ensure that women are informed early about the impact of substances on pregnancy outcomes may provide an important context for receipt of information. Additional research is required to identify effective means of changing behavior related to alcohol use during pregnancy rather than simply informing patients of the risks associated with prenatal alcohol use.

A majority of women (81.3%) agreed that physicians should be able to screen in the absence of consent. A recent survey of 847 obstetricians, pediatricians, and family practice physicians in the United States found that 61% to 75% agreed with mandatory screening for alcohol abuse; 43% to 55% agreed with mandatory screening for illicit drugs; and 52% favoured legislation that would make alcohol and drug use in pregnancy "child abuse" and grounds for removal to protective custody (256). Physician attitudes related to screening subjects without consent and the potential for child apprehension or limited treatment may harm the physician-patient relationship and create barriers to screening. The findings of this survey may indicate a conflict of clinician's attitudes with the ethical principles of beneficence, autonomy, and justice that should be considered in counseling or treating a pregnant woman who is using drugs or alcohol. Health care workers are obliged to promote the health of the pregnant woman and the fetus and minimize harm to both. At the same time, the health care worker must respect patient autonomy. Pregnant women have a right to be treated fairly and equally without infringement on their liberty. The key predictor of consent in multivariate models was a belief that women would not feel discriminated against if all infants were screened.

The risk of child apprehension was not a critical barrier to screening. Indeed, the difference in the proportion of mothers who agreed with screening with and without apprehension was 17%, potentially because the perceived benefit of screening and opportunity for treatment outweighs the potential risk that a child will be apprehended. Alternatively those who indicated that women should consent may not view child apprehension as a barrier. The outcome of 'child placed in care' was explored as the women in the focus groups had the perception that drug test results were used to make

decisions related to child apprehension. Of note, some child protection agencies in the US apply newborn screen results to make decisions related to child apprehension. A recent survey of 200 US State and County Child Protection Services found tremendous variation in neonatal screening programs (332). Some counties press criminal charges for positive screen results for cocaine, amphetamine/opiate, and cannabis, and some women may choose to deliver in a neighboring county without such policies to avoid screening or legal action (332). Importantly, a just society does not create an environment that limits a person's choices (e.g., minimal resources to address addiction during pregnancy) and then punish them for making a poor choice (252). There is no gold standard and no evidence base for how testing is performed, who is tested, and how test results are used (332). The authors of that survey called for empirically informed guidelines on drug and alcohol testing and standard effective and appropriate care for mothers and children (332).

A majority of women reported that their physician spoke to them about alcohol and drug use during pregnancy, with just over half recommending that no alcohol be consumed while pregnant. This is consistent with findings from a national survey on FAS prevention and diagnosis of Canadian physicians (272;273;333;334). Some women reported that their physicians told them that occasional or moderate alcohol use is fine, which is contrary to current American and Canadian guidelines (52-55). The number of women surveyed who believed that some alcohol use during pregnancy is safe (10%) is comparable to the proportion of physicians who tell their patients that some alcohol use is acceptable (9%). In addition, those surveyed felt that most women are unaware of the potential problems for fetal exposure to alcohol, suggesting missed opportunities for

learning and education. These factors may lead to a decreased perception of the threat of and susceptibility to an FASD.

This survey identified that 44.5% of women used some alcohol during pregnancy. Of note, approximately half of the women who drank during pregnancy did not identify alcohol use prior to pregnancy recognition as 'drinking during pregnancy' suggesting that there is variability in understanding of 'drinking during pregnancy' and the perceived risk associated with prenatal alcohol use prior to pregnancy recognition. Maternal rates of alcohol use during pregnancy can be compared to Alberta rates from the Physician Notification of Birth (PNOB), forms that are filled out and submitted within 24 hours of birth that rely upon care providers and birth attendants gathering information from either the women or the medical record. These data may be inaccurate due to biases related to social desirability, provider expectations and self-reported drug, alcohol and tobacco use and are most likely underestimations of true values (335). Alcohol use during pregnancy in Calgary recorded by PNOB was 2.3% for the year 2001, and 4.2% provincially for the years 1998 to 2000 (336). This is inconsistent with a 1998 US national survey that found that 58.8% of women drank while pregnant and 65.8% of women reporting alcohol use in their first trimester (75;337). Reported alcohol use in the third trimester in this US survey was higher at 53.9% versus 18.7% in the present survey (75). The prevalence of binge drinking in the year prior to pregnancy in this survey was 40% compared to 12.3% found among non-pregnant women in a 1999 US national survey, but is comparable to a recent rate of over 40% among female college students (338-341). The binge drinking rate of 12.3% is still higher than the Healthy People 2010 objectives of 6% in the previous month established by the US Department of Health and Human Services (53). The high

binge-drinking rate is of concern as prenatal drinking patterns are predictive of behavior during pregnancy. There is growing evidence that binge drinking in particular is harmful to the fetus (59;64;226;322).

This highlights the need for thorough history taking, preconceptional counseling, and more effective social marketing techniques to encourage women to abstain from alcohol if they are attempting to conceive or are pregnant. In addition, many fetuses are placed at risk given the following: 50% of women report binge drinking episodes; there is growing evidence for damage associated with binge alcohol exposure; up to 75% of pregnancies are unplanned and women continue to drink alcohol in their normal pattern until they recognize pregnancy at an average of 6-8 weeks; and there is a demonstrated susceptibility of the fetus to central nervous system insult at 21 days (228;229). There is an opportunity for further educational efforts for women and their care providers, a finding consistent with recent surveys on physician practice related to alcohol use.

Self-reported alcohol use during pregnancy did not decrease willingness to consent to screening in this study. In fact, women who self-reported alcohol use during pregnancy were more willing to consent to screening than women who denied alcohol use, which may reflect the perceived benefit of screening for these women. Women who reported alcohol use during pregnancy were more likely to support infant screening in virtually all questions and scenarios and were less likely to agree that it was a woman's right to refuse screening. They were also more likely to believe that a screening program would lead to less alcohol and drug use during pregnancy and would reduce the prevalence of FASD. The relationship between self-reported use of alcohol and

willingness to consent may be confounded by inaccurate report amongst women that denied alcohol use during pregnancy.

Women who would not consent to infant screening were older, more educated, less likely to report alcohol use during pregnancy, and less likely to think that there would be benefits associated with a screening program. In general, these women were professionals who may have seen screening as an invasion or violation of their privacy. These women were more knowledgeable of the risks of alcohol use. More important for these women perhaps was the perceived lack of benefit combined with the perceived lack of susceptibility (e.g., planned pregnancy in which alcohol was not consumed, non-drinker). However, older mothers may have established alcohol use patterns that are harder to change during pregnancy, and these women may have been less willing to self-report and at the same time less willing to consent to screening. This is consistent with an autonomous way of learning and viewing the world as described in 'Women's Ways of Knowing', in which the five stages of women's knowing are described (342). Older, professional, more educated women would conceive of truth and knowledge as private and personal and they would not depend on an external authority like a health care provider to make decisions. They may be less likely to disclose risk behaviors and less likely to consent to screening suggested by a healthcare provider. It would be important to reach this group with any screening program as the impact of prenatal alcohol exposure on fetal development appears is greater with advanced maternal age (77;184).

5.3.1 Generalizability, Strengths and Limitations

This cross-sectional survey of 1509 recently delivered women in an urban health care setting achieved a high participation rate of 78.4%. Those who took part were similar to all women giving birth in this health region in terms of age, income, ethnicity, parity, and education (299). Mean maternal age was 29.4 yrs in this region with the majority of births occurring to women aged 25 to 34 years. Consequently the findings are likely generalizable to similar urban centres in developed countries.

The data collection strategy attempted to capture all women giving birth in hospital. However, the sample did not capture women who were discharged early, did not speak English fluently, were in protective custody, whose children were being apprehended, or who developed maternal/neonatal complications, consequently some women at higher risk of substance use during pregnancy may have not been included. The questionnaire was designed to capture women's opinions at a point in time when they would potentially provide consent for newborn screening. Although women who consumed alcohol during pregnancy may have been less likely to participate, the rates of alcohol use during pregnancy were similar to those reported in Canadian and American population-based surveys, suggesting reasonable representation of the target population (229).

Chapter Six: Conclusions and Recommendations

In this chapter conclusions, recommendation and suggestions for future research for each of the study components will be discussed in separate sections. Overall conclusions from this research are as follows:

1. There was no association between maternal report of alcohol use and biomarker in meconium;
2. FAEE level was associated with child development and children with elevated levels of FAEE in meconium were at much greater risk of motor delay at 2 years of age; and
3. Women would consent to drug and alcohol screening of their newborns if there was evidence of effective treatment for children identified at risk for deficits.

6.1 Association between Maternal Self-report and Biomarker in Meconium

6.1.1 Conclusions

In this study of a maternity clinic population there was no evidence of association between self-report of alcohol use at several points pre- and post-natally, alcohol use in prior pregnancies, personal and family history of alcohol use, T-ACE scores, risk factors for drug and alcohol use during pregnancy and FAEE concentration in meconium by any of the examined cut-offs or by examining specific FAEEs. However, the rationale for this study was that maternal self-report is unreliable and therefore, the lack of association should not be surprising and a more relevant measure of association that should be examined is FAEE level and outcomes associated with prenatal alcohol exposure. A

screening program is not expected to be a method of assessing exposure but instead should be predictive of outcome. Women who reported alcohol use prior to or during pregnancy were not identified by FAEE analysis. There were few features that identified women whose infants had elevated concentrations of FAEEs in meconium. Infants with an elevated concentration of FAEE were more likely to come from high income families and to have mothers who reported frequent dairy consumption. This is the first study to report that male infants were more likely to have a positive sample than female infants.

Any relationship between FAEE concentration in meconium and alcohol use during pregnancy is likely complex and may be influenced by diet, ethnicity, genes of the mother and fetus, and the timing, dose and frequency of alcohol use. While there was no association between FAEE concentration and alcohol use, the T-ACE did identify women with lifestyle and behavioral characteristics consistent with prenatal alcohol use.

6.1.2 Recommendations

The following recommendations are made based on the study results.

1. Given that 9% of women reported using street drugs in the 12 months prior to pregnancy and 3% of women reported using street drugs during pregnancy it follows that there are opportunities for screening, counseling and intervention with all women regarding drug use in general and particularly during the perinatal period.
2. Over 30% of subjects reported a binge drinking pattern in the 12 months prior to pregnancy. Physicians should be aware of the prevalence of risk-drinking patterns among medically low risk women who are at risk for becoming pregnant and screen their patients appropriately.
3. Health care providers should be reassured that the T-ACE identifies women who report alcohol use during pregnancy and should be encouraged to adopt the T-ACE with all patients of during the childbearing years. Given that the T-ACE is incorporated into the prenatal record form in several jurisdictions, training efforts should be directed at proper use of this tool for screening, patient care and for initiating interventions that may decrease alcohol use during pregnancy. In addition, research should be directed at determining the value of improved use of existing tools.
4. History taking with periconceptional and prenatal patients should incorporate screening for abuse, personal history of alcohol problems, family history of alcohol problems, and low self-esteem. Over 30% of subjects reported a history of

abuse which was associated with prenatal smoking, alcohol and drug use among women in this study.

6.1.3 Future Research

Further research is needed on the following issues related to FAEE production and presence in meconium:

- Given that any relationship between FAEE concentration in meconium and alcohol use during pregnancy is likely complex and may be influenced by diet, ethnicity, genes of the mother and fetus, and timing, dose and frequency of alcohol use further research is required to understand factors that modify the production of FAEEs.
- Future studies could incorporate more assessments of maternal and infant physiologic, haematologic, endocrine, and genetic factors that may play a role in the production of FAEEs.
- There were several samples with very elevated FAEE concentrations and in most of these cases there was no report of alcohol use during pregnancy. It is critical to follow up the children with elevated FAEE concentrations to assess developmental outcomes.
- Primary, secondary and tertiary prevention efforts related to prenatal alcohol use remain an important goal. Research efforts should include methods to reduce the likelihood of prenatal alcohol exposure and encourage women to enter pregnancy in optimal health.

6.2 Biomarker Level and Child Development

6.2.1 Conclusions

In this study of a cohort assembled from low risk maternity clinic patients there was evidence of an association between motor delay as assessed by the BSID-II Psychomotor Development Index (PDI) at 2 years of age and concentration of FAEEs. Fatty acid ethyl ester concentration in meconium was correlated with PDI and 50% of the children who had a concentration of FAEE ≥ 500 ng/g in their meconium were found to have delayed motor development. On linear regression a concentration of FAEE ≥ 500 ng/g in meconium was associated with a decrease on the PDI of 9 points. In logistic regression analysis an OR of 26.9 was found for a FAEE concentration ≥ 5,000 ng/g after adjustment for infant sex, birth weight, report of daily alcohol use prior to pregnancy recognition and maternal age greater than 35 years at delivery, indicating that the odds of having motor delay for children with a FAEE concentration above this level was approximately 27 times that of children with lower levels of FAEE. Children with elevated FAEE were also more likely to have an Apgar score <7 at 1 minute, a lower weight at 12 months of age, and they tended to be slower in reaching their gross motor milestones. Daily alcohol use prior to pregnancy recognition and maternal age greater than 35 years at delivery were also associated with motor delay at 2 years of age. Female sex was a protective factor for motor delay.

There was no evidence of association between FAEE concentration and child mental development and behavioral outcomes as determined by BSDI-II MDI, ABAS, TABS and CBCL at 2 years of age. However, children with elevated levels of FAEE had

higher scores on the ABAS which did not reach statistical significance. There was also no evidence of association between T-ACE score and motor and mental development.

This is the first study to demonstrate that FAEE concentration in meconium is associated with motor delay in children at 2 years of age. In addition, the delay seen in motor development is consistent with that described previously in the literature for prenatal alcohol exposure. Psychomotor delay may be the most easily identified sign of developmental delay associated with prenatal alcohol exposure in children in this age range. However, any relationship between FAEE concentration in meconium and child development is likely complex. Approximately half of the subjects with elevated FAEE were not delayed. In addition, it is unclear whether FAEE in meconium is a biomarker for alcohol ingestion alone or if other factors may also lead to an elevated concentration of FAEE in meconium.

6.2.2 Recommendations

The following recommendations are made based on the study results.

1. There was evidence that there is an association between FAEE concentration in meconium and child motor development at 2 years of age. However, there is no evidence at this time that FAEE screening should be used clinically or that it should be implemented on a wider basis.
2. Without evidence of effective intervention, FAEE screening is not recommended. However, if done, a screening program could include standard follow up integrated into well baby visits with family physicians or public health nurses with all babies identified as at risk referred for further assessment. Resources for

mother and baby would also have to be available as part of a screening program. Drug and alcohol screening should not be stand alone tools used at birth but rather as part of an overall program of integrated pre-pregnancy, prenatal, postnatal and early childhood strategies.

3. There was an association between maternal report of daily alcohol use prior to pregnancy recognition and child motor development at 2 years of age emphasizing the need for physicians to take thorough drug and alcohol use histories from maternity patients and provide assistance or brief intervention as indicated.
4. The prevalence of alcohol use reported at 2 years post-partum is higher than at any time during pregnancy and at any point postpartum. This highlights the importance of revisiting alcohol use during pregnancy with a mother over time and documenting this. If a child does demonstrate delay or worrisome features a documented history of alcohol use during pregnancy can be crucial for further appropriate referral.

6.2.3 Future Research

Further research is required to understand factors that modify the production of FAEE and the utility of FAEE screening:

- Given that an association of clinically significant magnitude is seen it is important to reproduce these results and build in additional studies to understand the basic biology, clinical utility of FAEE testing, and protective factors for child development for children identified by elevated concentration of FAEE.

- The mothers and the children from this study should be followed up over time to understand if motor differences seen at 2 years of age persist or if other differences become more pronounced. In addition, the remaining 32 children from the original cohort should be followed up to see if there are differences seen in a larger sample in the domains of behavior and cognition. A follow up of the children from the MEC Study is planned for 6 years of age.
- Given the deficits in early language that have been described in the literature, language assessments of the children should be completed to determine if there are differences between children by FAEE group or maternal self-report of prenatal alcohol use. This analysis will be done for the subjects of this study.
- Further research is required to understand the association between maternal genetic, biologic, behavioral and lifestyle factors that may contribute to FAEE production in meconium and how that impacts child development.
- A large trial of maternity patients that incorporates prospective collection of lifestyle and demographic variables with the collection of blood samples for genetic analysis coupled with an intervention arm for children identified at risk by FAEE or report of elevated level of alcohol use should be considered. With multiple follow up steps the natural progression of this deficit could be better understood. In addition, the benefit of different interventions around psychomotor integration and therapy could be examined.
- Mechanisms to best follow up children identified as at risk require development and pilot testing. Potentially, these could this be integrated into well baby visits,

however, the feasibility of increasing the work load of health care providers requires planning and investigation.

- Further research is required to understand the potential effectiveness of a screening program that could involve FAEE screening of meconium and early interventions for mother and child. This information is crucial for the development of an effective screening program.

6.3 Maternal Willingness to Consent

6.3.1 Conclusions

Women would support and consent to a screening program if there was evidence that screening could make a difference for mom and baby, and appropriate resources were available to optimize development. Less important was consent in the testing process. Women indicated that universal screening decreases discrimination associated with selective screening. Women at risk of an alcohol exposed pregnancy as identified by a positive T-ACE score, binge drinking prior to pregnancy, would support universal screening, whereas more highly educated older women were less likely to support universal screening. Women most likely to benefit from early identification of risky drinking during pregnancy would engage in a screening program.

A screening program that women would participate in would have the following qualities:

- Universal;
- Information about screening would be provided early in pregnancy and prior to sample collection;
- Informed consent;
- Access to services to mitigate the effects of alcohol and drug exposure for the infant;
- Access to services for mothers who require them to address issues of addiction; and
- Evidence-based.

6.3.2 Recommendations

The following recommendations are made based on the study results.

1. A screening program would have to include an information and dissemination component to address women's concerns and describe how a test results would be used and the effectiveness of any treatment for children identified as at risk. Mothers would have to be reassured that a test result would not be used to build a case for infant apprehension. Information about screening could be presented at the first prenatal visit and prior to sample collection. This discussion could be an effective intervention for women to eliminate alcohol use during pregnancy and identify women that would benefit from additional interventions to reduce problem-drinking during pregnancy.
2. There is clearly a need for further educational efforts for women and their care providers, a finding consistent with recent surveys on physician practice related to alcohol use. All women of reproductive age should have alcohol use assessed and be counseled to abstain prior to trying to conceive as per current clinical practice guidelines.

6.3.3 Future Research

There is a need for evidence-based guidelines on drug and alcohol screening, reporting, and follow up to provide a standard of effective and appropriate care for mothers and children.

- There exist opportunities for education and research in the area of social marketing and behavior change related to alcohol use in pregnancy, as well as

generating the crucial evidence related to the effectiveness of early diagnosis and intervention.

- An opportunity exists to arrive at a national consensus on consent in the screening of infants in the area of drugs and alcohol, genetic, metabolic, and hearing.
- Methods to prepare and support physicians in providing preconception counseling to women of childbearing age should be evaluated. There is an opportunity for improved history taking, preconceptional counseling, and for more effective social marketing techniques to encourage women to abstain from alcohol if they are attempting to conceive or are pregnant.
- Methods to engage those resistant to screening should be investigated. Women that are well educated are not at decreased risk of problem drinking during pregnancy.

References

(1) Barr HM, Streissguth AP, Martin DC, Herman CS. Infant size at 8 months of age: relationship to maternal use of alcohol, nicotine, and caffeine during pregnancy. Pediatrics 1984; 74(3):336-341.

(2) Health Canada. Joint statement: prevention of fetal alcohol syndrome (FAS), fetal alcohol effects (FAE) in Canada. Cat. No. H39-348/1996E. 1996. Ottawa, Health Canada.

(3) Smitherman CH. The Lasting Impact of Fetal Alcohol Syndrome and Fetal Alcohol Effect on Children and Adolescents. Journal of Pediatric Health Care 1994; 8(3):121-126.

(4) Health Canada. Best Practices: Fetal Alcohol Syndrome / Fetal Alcohol Effects and the effects of other substance use during pregnancy. Cat. No. H49-156/1-2001E, ISBN 0-662-30212-5. 2001. Ottawa, Minister of Public Works and Government Services Canada.

(5) Streissguth AP. Understanding the occurrence of secondary disabilities in clients with Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Effects (FAE). 1996. Seattle, WA, University of Washington School of Medicine.

(6) Streissguth AP, O'Malley K. Neuropsychiatric implications and long-term consequences of fetal alcohol spectrum disorders. Seminars in Clinical Neuropsychiatry 2000; 5(3):177-190.

(7) Abel EL. An update on incidence of FAS: FAS is not an equal opportunity birth defect. Neurotoxicology & Teratology 1995; 17(4):437-443.

(8) Abel EL, Sokol RJ. A revised conservative estimate of the incidence of FAS and its economic impact. Alcohol Clin Exp Res 1991; 15(3):514-524.

(9) Clarren SK, Randels SP, Sanderson M, Fineman RM. Screening for fetal alcohol syndrome in primary schools: a feasibility study. Teratology 2001; 63(1):3-10.

(10) Miller L, Tolliver R, Druschel C, Fox D, Schoellhorn J, Podvin D et al. Fetal alcohol syndrome--Alaska, Arizona, Colorado, and New York, 1995-1997. MMWR - Morbidity & Mortality Weekly Report 2002; 51(20):433-435.

(11) Weiss M, Cronk CE, Mahkorn S, Glysch R, Zirbel S. The Wisconsin Fetal Alcohol Syndrome Screening Project. WMJ 2004; 103(5):53-60.

(12) Sampson PD, Streissguth AP, Bookstein FL, Little RE, Clarren SK, Dehaene P et al. Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder. Teratology 1997; 56(5):317-326.

(13) Robinson GC, Conry JL, Conry RF. Clinical profile and prevalence of fetal alcohol syndrome in an isolated community in British Columbia. CMAJ 1987; 137:203-207.

(14) Williams RJ, Odaibo FS, McGee JM. Incidence of fetal alcohol syndrome in northeastern Manitoba. Can J Public Health 1999; 90(3):192-194.

(15) May PA, Brooke L, Gossage JP, Croxford J, Adnams C, Jones KL et al. Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. American Journal of Public Health 2000; 90(12):1905-1912.

(16) May PA, Gossage JP, Marais AS, Adnams CM, Hoyme HE, Jones KL et al. The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. Drug Alcohol Depend 2007; 88(2-3):259-271.

(17) Fast DK, Conry J, Loock CA. Identifying fetal alcohol syndrome among youth in the criminal justice system. J Dev Behav Pediatr 1999; 20(5):370-372.

(18) May PA, Fiorentino D, Phillip GJ, Kalberg WO, Eugene HH, Robinson LK et al. Epidemiology of FASD in a province in Italy: Prevalence and characteristics of children in a random sample of schools. Alcohol Clin Exp Res 2006; 30(9):1562-1575.

(19) Bennett AD. Perinatal substance abuse and the drug-exposed neonate. Advance for Nurse Practitioners 1999; 7(5):32-36.

(20) Singer LT, Salvator A, Arendt R, Minnes S, Farkas K, Kliegman R. Effects of cocaine/polydrug exposure and maternal psychological distress on infant birth outcomes. Neurotoxicol Teratol 2002; 24(2):127-135.

(21) Singer LT, Minnes S, Short E, Arendt R, Farkas K, Lewis B et al. Cognitive outcomes of preschool children with prenatal cocaine exposure. JAMA 2004; 291(20):2448-2456.

(22) Abel EL. Fetal alcohol syndrome and fetal alcohol effects. New York: Plenum Press, 1984.

(23) Alberta Medical Association. Guideline for the diagnosis of fetal alcohol syndrome (FAS). 1999. Edmonton (AB).

(24) Alberta Medical Association. Recommendations: Prevention of Fetal Alcohol Syndrome (FAS). 1999. Edmonton (AB).

(25) Alberta Medical Association. Preface to the prevention & diagnosis of fetal alcohol syndrome (FAS). 1999. Edmonton (AB).

(26) Astley SJ, Clarren SK. A fetal alcohol syndrome screening tool. Alcohol Clin Exp Res 1995; 19(6):1565-1571.

(27) Astley SJ, Clarren SK. A case definition and photographic screening tool for the facial phenotype of fetal alcohol syndrome. J Pediatr 1996; 129(1):33-41.

(28) Astley SJ, Clarren SK. Diagnostic Guide for Fetal Alcohol Syndrome and Related Conditions: The 4-Digit Diagnostic Code. 2nd edition, 1-39. 1999. Seattle, FAS Diagnostic and Prevention Network, University of Washington.

(29) Astley SJ, Clarren SK. Diagnosing the full spectrum of fetal alcohol exposed individuals: introducing the 4-digit diagnostic code. Alcohol Alcohol 2000; 35(4):400-410.

(30) Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. Lancet 1973; 2(7836):999-1001.

(31) Streissguth AP, Barr HM, Martin DC. Offspring effects and pregnancy complications related to self-reported maternal alcohol use. Developmental Pharmacology & Therapeutics 1982; 5(1-2):21-32.

(32) Streissguth AP, Barr HM, Sampson PD. Moderate prenatal alcohol exposure: effects on child IQ and learning problems at age 7 1/2 years. Alcohol Clin Exp Res 1990; 14(5):662-669.

(33) Streissguth AP. Fetal alcohol syndrome: a guide for families and communities. Baltimore, Maryland: Paul H. Publishing Co., 1997.

(34) Astley SJ. Comparison of the 4-digit diagnostic code and the Hoyme diagnostic guidelines for fetal alcohol spectrum disorders. Pediatrics 2006; 118(4):1532-1545.

(35) Chudley AE, Conry J, Cook JL, Loock C, Rosales T, LeBlanc N. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. CMAJ 2005; 172(5 Suppl):S1-S21.

(36) Astley SJ, Bailey D, Talbot C, Clarren SK. Fetal alcohol syndrome (FAS) primary prevention through FAS diagnosis: II. A comprehensive profile of 80 birth mothers of children with FAS. Alcohol Alcohol 2000; 35(5):509-519.

(37) Baer JS, Barr HM, Bookstein FL, Sampson PD, Streissguth AP. Prenatal alcohol exposure and family history of alcoholism in the etiology of adolescent alcohol problems. Journal of Studies on Alcohol 1998; 59(5):533-543.

(38) Baer JS, Sampson PD, Barr HM, Connor PD, Streissguth AP. A 21-year longitudinal analysis of the effects of prenatal alcohol exposure on young adult drinking. Archives of General Psychiatry 2003; 60(4):377-385.

(39) Coles CD, Platzman KA, Raskind-Hood CL, Brown RT, Falek A, Smith IE. A comparison of children affected by prenatal alcohol exposure and attention deficit, hyperactivity disorder. Alcohol Clin Exp Res 1997; 21(1):150-161.

(40) Jacobson S, Jacobson J. FAS/FAE and its impact on psychosocial child development. Tremblay RE, Barr RG, Peters R, editors. Encyclopedia on Early Childhood Develoment [online]. 1-7. 14-2-2003. Montreal, Centre of Excellence for Early Childhood Development.

(41) Kerns KA, Don A, Mateer CA, Streissguth AP. Cognitive deficits in nonretarded adults with fetal alcohol syndrome. Journal of Learning Disabilities 1997; 30(6):685-693.

(42) O'Connor MJ, Shah B, Whaley S, Cronin P, Gunderson B, Graham J. Psychiatric illness in a clinical sample of children with prenatal alcohol exposure. American Journal of Drug & Alcohol Abuse 2002; 28(4):743-754.

(43) Olson HC, Streissguth AP, Sampson PD, Barr HM, Bookstein FL, Thiede K. Association of prenatal alcohol exposure with behavioral and learning problems in early adolescence. Journal of the American Academy of Child & Adolescent Psychiatry 1997; 36(9):1187-1194.

(44) Puttler LI, Zucker RA, Fitzgerald HE, Bingham CR. Behavioral outcomes among children of alcoholics during the early and middle childhood years: familial subtype variations. Alcohol Clin Exp Res 1998; 22(9):1962-1972.

(45) Steinhausen HC, Nestler V, Spohr HL. Development of psychopathology of children with the fetal alcohol syndrome. J Dev Behav Pediatr 1982; 3(2):49-54.

(46) Streissguth AP. Maternal drinking and the outcome of pregnancy: implications for child mental health. American Journal of Orthopsychiatry 1977; 47(3):422-431.

(47) Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, Young JK. Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. J Dev Behav Pediatr 2004; 25(4):228-238.

(48) Alberta Health and Wellness. Health is Everyone's Business: A Snapshot of Some of Alberta's Wellness Inititatives. 2000. Edmonton, AB, Alberta Health and Wellness - Communication Branch.

(49) Stade BC, Stevens B, Ungar WJ, Beyene J, Koren G. Health-related quality of life of Canadian children and youth prenatally exposed to alcohol. Health Qual Life Outcomes 2006; 4:81.:81.

(50) Abel EL, Sokol RJ. A revised estimate of the economic impact of fetal alcohol syndrome. Recent Developments in Alcoholism 1991; 9:117-125.

(51) Stade BC. The burden of prenatal exposure to alcohol: Measurement of quality of life and costs. University of Toronto, 2003.

(52) Surgeon general's advisory on alcohol and pregnancy. FDA Drug Bull 1981; 11(2):9-10.

(53) Healthy people 2010. Departement of health and Human services 2000.

(54) American Academy of Pediatrics Committee on Substance Abuse and Committee on Children With Disabilities. Fetal alcohol syndrome and alcohol-related neurodevelopmental disorders. Pediatrics 2000; 106(2 Pt 1):358-361.

(55) Canadian Paediatric Society. Fetal alcohol syndrome - Position Statement (II 2002-01). Paediatric Child Health 2002; 7(3):161-174.

(56) Abel EL, Sokol RJ. Maternal and fetal characteristics affecting alcohol's teratogenicity. [Review] [54 refs]. Neurobehavioral Toxicology & Teratology 1986; 8(4):329-334.

(57) Abel EL, Hannigan JH. Maternal risk factors in fetal alcohol syndrome: provocative and permissive influences.[erratum appears in Neurotoxicol Teratol 1995 Nov-Dec;17(6):689]. [Review] [327 refs]. Neurotoxicology & Teratology 1995; 17(4):445-462.

(58) Allebeck P, Olsen J. Alcohol and fetal damage. [Review] [43 refs]. Alcohol Clin Exp Res 1998; 22(7 Suppl):329S-332S.

(59) Bailey BN, Delaney-Black V, Covington CY, Ager J, Janisse J, Hannigan JH et al. Prenatal exposure to binge drinking and cognitive and behavioral outcomes at age 7 years. American Journal of Obstetrics & Gynecology 2004; 191(3):1037-1043.

(60) Bearer CF. Mechanisms of brain injury: L1 cell adhesion molecule as a target for ethanol-induced prenatal brain injury. [Review] [82 refs]. Seminars in Pediatric Neurology 2001; 8(2):100-107.

(61) Hard ML, Abdolell M, Robinson BH, Koren G. Gene-expression analysis after alcohol exposure in the developing mouse. Journal of Laboratory & Clinical Medicine 2005; 145(1):47-54.

(62) Maier SE, West JR. Drinking patterns and alcohol-related birth defects. Alcohol Research & Health: the Journal of the National Institute on Alcohol Abuse & Alcoholism 2001; 25(3):168-174.

(63) Menegola E, Broccia ML, Di Renzo F, Giavini E. Acetaldehyde in vitro exposure and apoptosis: a possible mechanism of teratogenesis. Alcohol 2001; 23(1):35-39.

(64) Nulman I, Rovet J, Kennedy D, Wasson C, Gladstone J, Fried S et al. Binge alcohol consumption by non-alcohol-dependent women during pregnancy affects child behaviour, but not general intellectual functioning; a prospective controlled study. Archives of Women's Mental Health 2004; 7(3):173-181.

(65) O'Connor MJ, Brill NJ, Sigman M. Alcohol use in primiparous women older than 30 years of age: relation to infant development. Pediatrics 1986; 78(3):444-450.

(66) Olney JW, Wozniak DF, Farber NB, Jevtovic-Todorovic V, Bittigau P, Ikonomidou C. The enigma of fetal alcohol neurotoxicity. Annals of Medicine 2002; 34(2):109-119.

(67) Zajac CS, Abel EL. Animal models of prenatal alcohol exposure. [Review] [131 refs]. Int J Epidemiol 1992; 21 Suppl 1:S24-S32.

(68) Bearer CF. Markers to detect drinking during pregnancy. [Review] [36 refs]. Alcohol Research & Health: the Journal of the National Institute on Alcohol Abuse & Alcoholism 2001; 25(3):210-218.

(69) Health Canada. Canadian Perinatal Surveillance System, alcohol and pregnancy. http://www.hc-sc.gc.ca/pphb-dgspsp/rhs-ssg/factshts/alcprg_e.html . 1998.

(70) Health Canada. Canadian Perinatal Health Report, 2000. ISBN 0-662-29309-6, Cat. No. H49-142/2000E. 2000. Ottawa, Minister of Public Works and Government Services Canada.

(71) Health Canda. Perinatal Health Indicators for Canada: A Resource Manual. Cat. No. H49-135/2000E, ISBN 0-662-28850-5. 2000. Ottawa, Minister of Public Works and Government Services Canada.

(72) Ebrahim SH, Luman ET, Floyd RL, Murphy CC, Bennett EM, Boyle CA. Alcohol consumption by pregnant women in the United States during 1988-1995. Obstetrics & Gynecology 1998; 92(2):187-192.

(73) Ebrahim SH, Diekman ST, Floyd RL, Decoufle P. Comparison of binge drinking among pregnant and nonpregnant women, United States, 1991-1995. American Journal of Obstetrics & Gynecology 1999; 180(1 Pt 1):1-7.

(74) Ebrahim SH, Gfroerer J. Pregnancy-related substance use in the United States during 1996-1998. Obstetrics & Gynecology 2003; 101(2):374-379.

(75) US Department of Health and Human Services. Summary of findings from the 1999 National Household Survey on Drug Abuse. 2000. Washington, DC, US Department of Health and Human Services.

(76) Barr HM, Streissguth AP. Identifying maternal self-reported alcohol use associated with fetal alcohol spectrum disorders. Alcohol Clin Exp Res 2001; 25(2):283-287.

(77) Gladstone J, Levy M, Nulman I, Koren G. Characteristics of pregnant women who engage in binge alcohol consumption. CMAJ Canadian Medical Association Journal 1997; 156(6):789-794.

(78) Little RE, Uhl CN, Labbe RF, Abkowitz JL, Phillips EL. Agreement between laboratory tests and self-reports of alcohol, tobacco, caffeine, marijuana and other drug use in post-partum women. Social Science & Medicine 1986; 22(1):91-98.

(79) Clarren SK. Identification of Children with Fetal Alcohol Syndrome and Opportunity for Refferal of their Mothers for Primary Prevention - Washington, 1993-1997. MMWR 1998; 47(40):861-865.

(80) Streissguth AP, Aase JM, Clarren SK, Randels SP, LaDue RA, Smith DF. Fetal alcohol syndrome in adolescents and adults. JAMA 1991; 265(15):1961-1967.

(81) Clarren SK, Smith DW. The fetal alcohol syndrome. N Engl J Med 1978; 298(19):1063-1067.

(82) Chasnoff IJ. Drug use and women: establishing a standard of care. Annals of the New York Academy of Sciences 1989; 562:208-210.

(83) Chasnoff IJ, Landress HJ, Barrett ME. The prevalence of illicit-drug or alcohol use during pregnancy and discrepancies in mandatory reporting in Pinellas County, Florida. New Engl J Med 1990; 322(17):1202-1206.

(84) Teagle SE, Brindis CD. Substance use among pregnant adolescents: a comparison of self-reported use and provider perception. Journal of Adolescent Health 1998; 22(3):229-238.

(85) Koren G, Chan D, Klein J, Karaskov T. Estimation of fetal exposure to drugs of abuse, environmental tobacco smoke, and ethanol. Ther Drug Monit 2002; 24(1):23-25.

(86) Chasnoff IJ, Neuman K, Thornton C, Callaghan MA. Screening for substance use in pregnancy: A practical approach for the primary care physician. American Journal of Obstetrics & Gynecology 2001; 184(4):752-758.

(87) McNamara TK, Orav EJ, Wilkins-Haug L, Chang G. Risk during pregnancy--self-report versus medical record. American Journal of Obstetrics & Gynecology 2005; 193(6):1981-1985.

(88) Bradley KA, Boyd-Wickizer J, Powell SH, Burman ML. Alcohol screening questionnaires in women: a critical review. JAMA 1998; 280(2):166-171.

(89) Sokol RJ, Martier SS, Ager JW. The T-ACE questions: practical prenatal detection of risk-drinking. American Journal of Obstetrics & Gynecology 1989; 160(4):863-868.

(90) Chang G, Wilkins-Haug L, Berman S, Goetz MA, Behr H, Hiley A. Alcohol use and pregnancy: improving identification. Obstet Gynecol 1998; 91(6):892-898.

(91) Chang G. Alcohol-screening instruments for pregnant women. Alcohol Research & Health: the Journal of the National Institute on Alcohol Abuse & Alcoholism 2001; 25(3):204-209.

(92) Bearer CF, Moore C, Salvatore A, Lee S, Buck K, Singer L. Meconium FAEE: Development of a biological marker. Alcoholism: Clinical Experience and Research 1998; 22(3):103A.

(93) Bearer CF, Lee S, Salvator AE, Minnes S, Swick A, Yamashita T et al. Ethyl linoleate in meconium: a biomarker for prenatal ethanol exposure. Alcohol Clin Exp Res 1999; 23(3):487-493.

(94) Bearer CF, Jacobson JL, Jacobson SW, Barr D, Croxford J, Molteno CD et al. Validation of a new biomarker of fetal exposure to alcohol. J Pediatr 2003; 143(4):463-469.

(95) Klein J, Karaskov T, Koren G. Fatty acid ethyl esters: a novel biologic marker for heavy in utero ethanol exposure: a case report. Ther Drug Monit 1999; 21(6):644-646.

(96) Moore C, Negrusz A, Lewis D. Determination of drugs of abuse in meconium. Journal of Chromatography 1998; B, Biomedical Sciences & Applications. 713(1):137-146.

(97) Moore C, Jones J, Lewis D, Buchi K. Prevalence of fatty acid ethyl esters in meconium specimens. Clinical Chemistry 2003; 49(1):133-136.

(98) Moore CM, Lewis D. Fatty acid ethyl esters in meconium: biomarkers for the detection of alcohol exposure in neonates. Clinica Chimica Acta 2001; 312(1-2):235-237.

(99) Ostrea EM, Jr., Brady M, Gause S, Raymundo AL, Stevens M. Drug screening of newborns by meconium analysis: a large-scale, prospective, epidemiologic study. Pediatrics 1992; 89(1):107-113.

(100) Ostrea EM, Jr. Testing for exposure to illicit drugs and other agents in the neonate: a review of laboratory methods and the role of meconium analysis. Curr Probl Pediatr 1999; 29(2):37-56.

(101) Chan D, Knie B, Boskovic R, Koren G. Placental handling of fatty acid ethyl esters: perfusion and subcellular studies. Journal of Pharmacology & Experimental Therapeutics 2004; 310(1):75-82.

(102) Laposata M. Fatty acid ethyl esters: ethanol metabolites which mediate ethanol-induced organ damage and serve as markers of ethanol intake. Prog Lipid Res 1998; 37(5):307-316.

(103) Laposata M. Fatty acid ethyl esters: current facts and speculations. Prostaglandins Leukot Essent Fatty Acids 1999; 60(5-6):313-315.

(104) Laposata M. Fatty acid ethyl esters: nonoxidative ethanol metabolites with emerging biological and clinical significance. Lipids 1999; 34 Suppl:S281-S285.

(105) Ostrea EM, Jr., Hernandez JD, Bielawski DM, Kan JM, Leonardo GM, Abela MB et al. Fatty Acid ethyl esters in meconium: are they biomarkers of fetal alcohol exposure and effect? Alcohol Clin Exp Res 2006; 30(7):1152-1159.

(106) Best CA, Laposata M. Fatty acid ethyl esters: toxic non-oxidative metabolites of ethanol and markers of ethanol intake. Frontiers in Bioscience 2003; 8:e202-e217.

(107) Bearer CF, Santiago LM, O'Riordan MA, Buck K, Lee SC, Singer LT. Fatty Acid ethyl esters: quantitative biomarkers for maternal alcohol consumption. J Pediatr 2005; 146(6):824-830.

(108) Chan D, Klein J, Karaskov T, Koren G. Fetal exposure to alcohol as evidenced by fatty acid ethyl esters in meconium in the absence of maternal drinking history in pregnancy. Ther Drug Monit 2004; 26(5):474-481.

(109) Chan D, Klein J, Koren G. Validation of meconium fatty acid ethyl esters as biomarkers for prenatal alcohol exposure. J Pediatr 2004; 144(5):692.

(110) Annas GJ. Testing poor pregnant patients for cocaine--physicians as police investigators. New Engl J Med 2001; 344(22):1729-1732.

(111) British Columbia Provincial Perinatal Steering Committee. Substance use guideline 3: General management of pregnant substance using women. British Columbia Reproductive Care Program . 1999. 5-6-2003.

(112) MacMahon JR. Perinatal substance abuse: the impact of reporting infants to child protective services. Pediatrics 1997; 100(5):E1.

(113) Wilson JM, Jungner G. Principles and practice of screening for disease. Public Health Papers 1968; 34:26-39.

(114) Hicks M, Sauve R, Lyon A, Clarke M, Tough S. Alcohol use and abuse in pregnancy: An evaluation of the merits of screening. Can Child Adol Psych Rev 12, 77-80.

(115) Lemoine P ea. Les Enfants des parents alcooliques: Anomalies observes apropos de 127 cas. Ouest Medical 1968; 21:476-482.

(116) Abel EL, Sokol RJ. Maternal and fetal characteristics affecting alcohol's teratogenicity. Neurobehavioral Toxicology & Teratology 1986; 8(4):329-334.

(117) Hard ML, Einarson TR, Koren G. The role of acetaldehyde in pregnancy outcome after prenatal alcohol exposure. Ther Drug Monit 2001; 23(4):427-434.

(118) Abel EL. Alcohol-induced changes in blood gases, glucose, and lactate in pregnant and nonpregnant rats. Alcohol 1996; 13(3):281-285.

(119) Mattson SN, Schoenfeld AM, Riley EP. Teratogenic effects of alcohol on brain and behavior. Alcohol Research & Health: the Journal of the National Institute on Alcohol Abuse & Alcoholism 2001; 25(3):185-191.

(120) Malanga CJ, III, Kosofsky BE. Mechanisms of action of drugs of abuse on the developing fetal brain. Clin Perinatol 1999; 26(1):17-37.

(121) Clarren SK, Alvord EC, Jr., Sumi SM, Streissguth AP, Smith DW. Brain malformations related to prenatal exposure to ethanol. J Pediatr 1978; 92(1):64-67.

(122) Astley SJ, Clarren SK. Diagnostic guide for fetal alcohol syndrome and related conditions: The 4-Digit Diagnostic Code. 2nd edition, 1-39. 1999. Seattle, FAS Diagnostic and Prevention Network, University of Washington.

(123) Astley SJ, Clarren SK. Measuring the facial phenotype of individuals with prenatal alcohol exposure: correlations with brain dysfunction. Alcohol Alcohol 2001; 36(2):147-159.

(124) Astley SJ, Stachowiak J, Clarren SK, Clausen C. Application of the fetal alcohol syndrome facial photographic screening tool in a foster care population. J Pediatr 2002; 141(5):712-717.

(125) Parnell SE, Dehart DB, Wills TA, Chen SY, Hodge CW, Besheer J et al. Maternal oral intake mouse model for fetal alcohol spectrum disorders: ocular defects as a measure of effect. Alcohol Clin Exp Res 2006; 30(10):1791-1798.

(126) Sulik KK. Genesis of alcohol-induced craniofacial dysmorphism. Exp Biol Med (Maywood) 2005; 230(6):366-375.

(127) Dunty WC, Jr., Zucker RM, Sulik KK. Hindbrain and cranial nerve dysmorphogenesis result from acute maternal ethanol administration. Dev Neurosci 2002; 24(4):328-342.

(128) Day NL, Zuo Y, Richardson GA, Goldschmidt L, Larkby CA, Cornelius MD. Prenatal alcohol use and offspring size at 10 years of age. Alcohol Clin Exp Res 1999; 23(5):863-869.

(129) Day NL, Richardson G, Robles N, Sambamoorthi U, Taylor P, Scher M et al. Effect of prenatal alcohol exposure on growth and morphology of offspring at 8 months of age. Pediatrics 1990; 85(5):748-752.

(130) Day NL, Richardson GA, Geva D, Robles N. Alcohol, marijuana, and tobacco: effects of prenatal exposure on offspring growth and morphology at age six. Alcohol Clin Exp Res 1994; 18(4):786-794.

(131) Fried PA, O'Connell CM, Watkinson B. 60- and 72-month follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol: cognitive and language assessment. J Dev Behav Pediatr 1992; 13(6):383-391.

(132) Fried PA, Watkinson B, Gray R. A follow-up study of attentional behavior in 6-year-old children exposed prenatally to marihuana, cigarettes, and alcohol. Neurotoxicol Teratol 1992; 14(5):299-311.

(133) Fried PA, Watkinson B. 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol. J Dev Behav Pediatr 1990; 11(2):49-58.

(134) Fried PA, Watkinson B. 12- and 24-month neurobehavioural follow-up of children prenatally exposed to marihuana, cigarettes and alcohol. Neurotoxicol Teratol 1988; 10(4):305-313.

(135) Fried PA, Watkinson B, Dillon RF, Dulberg CS. Neonatal neurological status in a low-risk population after prenatal exposure to cigarettes, marijuana, and alcohol. J Dev Behav Pediatr 1987; 8(6):318-326.

(136) Fried PA, O'Connell CM. A comparison of the effects of prenatal exposure to tobacco, alcohol, cannabis and caffeine on birth size and subsequent growth. Neurotoxicol Teratol 1987; 9(2):79-85.

(137) Coles CD, Smith I, Fernhoff PM, Falek A. Neonatal neurobehavioral characteristics as correlates of maternal alcohol use during gestation. Alcohol Clin Exp Res 1985; 9(5):454-460.

(138) Jacobson JL, Jacobson SW, Sokol RJ. Effects of Prenatal Exposure to Alcohol, Smoking, and Illicit Drugs on Postpartum Somatic Growth. Alcohol Clin Exp Res 1994; 18(2):317-323.

(139) Jacobson SW, Jacobson JL, Sokol RJ, Martier SS, Ager JW. Prenatal alcohol exposure and infant information processing ability. Child Development 1993; 64(6):1706-1721.

(140) Ho E, Collantes A, Kapur BM, Moretti M, Koren G. Alcohol and breast feeding: calculation of time to zero level in milk. Biology of the Neonate 2001; 80(3):219-222.

(141) Koren G. Drinking alcohol while breastfeeding. Will it harm my baby? Canadian Family Physician 2002; 48:39-41.

(142) Little RE, Anderson KW, Ervin CH, Worthington-Roberts B, Clarren SK. Maternal alcohol use during breast-feeding and infant mental and motor development at one year. N Engl J Med 1989; 321(7):425-430.

(143) Little RE, Northstone K, Golding J, ALSPAC Study Team. Alcohol, breastfeeding, and development at 18 months. Pediatrics 2002; 109(5):E72.

(144) Wozniak DF, Hartman RE, Boyle MP, Vogt SK, Brooks AR, Tenkova T et al. Apoptotic neurodegeneration induced by ethanol in neonatal mice is associated with profound learning/memory deficits in juveniles followed by progressive functional recovery in adults. Neurobiol Dis 2004; 17(3):403-414.

(145) Dikranian K, Qin YQ, Labruyere J, Nemmers B, Olney JW. Ethanol-induced neuroapoptosis in the developing rodent cerebellum and related brain stem structures. Brain Res Dev Brain Res 2005; 155(1):1-13.

(146) Savage C, Wray J, Ritchey PN, Sommers M, Dyehouse J, Fulmer M. Current screening instruments related to alcohol consumption in pregnancy and a

proposed alternative method. JOGNN - Journal of Obstetric, Gynecologic, & Neonatal Nursing 2003; 32(4):437-446.

(147) Hamilton DA, Kodituwakku P, Sutherland RJ, Savage DD. Children with Fetal Alcohol Syndrome are impaired at place learning but not cued-navigation in a virtual Morris water task. Behav Brain Res 2003; 143(1):85-94.

(148) Hamilton DA, Akers KG, Weisend MP, Sutherland RJ. How do room and apparatus cues control navigation in the Morris water task? Evidence for distinct contributions to a movement vector. J Exp Psychol Anim Behav Process 2007; 33(2):100-114.

(149) Kodituwakku PW, Handmaker NS, Cutler SK, Weathersby EK, Handmaker SD. Specific impairments in self-regulation in children exposed to alcohol prenatally. Alcohol Clin Exp Res 1995; 19(6):1558-1564.

(150) Kodituwakku PW, Kalberg W, May PA. The effects of prenatal alcohol exposure on executive functioning. Alcohol Research & Health: the Journal of the National Institute on Alcohol Abuse & Alcoholism 2001; 25(3):192-198.

(151) Mattson SN, Riley EP, Jernigan TL, Garcia A, Kaneko WM, Ehlers CL et al. A decrease in the size of the basal ganglia following prenatal alcohol exposure: a preliminary report. Neurotoxicol Teratol 1994; 16(3):283-289.

(152) Mattson SN, Riley EP, Sowell ER, Jernigan TL, Sobel DF, Lyons JK. A decrease in the size of the basal ganglia in children with fetal alcohol syndrome. Alcohol Clin Exp Res 1996; 20(6):1088-1093.

(153) Mattson SN, Riley EP, Delis DC, Stern C, Lyons JK. Verbal learning and memory in children with fetal alcohol syndrome. Alcohol Clin Exp Res 1996; 20(5):810-816.

(154) Mattson SN, Riley EP. A review of the neurobehavioral deficits in children with fetal alcohol syndrome or prenatal exposure to alcohol. Alcohol Clin Exp Res 1998; 22(2):279-294.

(155) Mattson SN, Goodman AM, Caine C, Delis DC, Riley EP. Executive functioning in children with heavy prenatal alcohol exposure. Alcohol Clin Exp Res 1999; 23(11):1808-1815.

(156) Riley EP, Mattson SN, Sowell ER, Jernigan TL, Sobel DF, Jones KL. Abnormalities of the corpus callosum in children prenatally exposed to alcohol. Alcohol Clin Exp Res 1995; 19(5):1198-1202.

(157) Riley EP, McGee CL, Sowell ER. Teratogenic effects of alcohol: a decade of brain imaging. American Journal of Medical Genetics 2004; Part C, Seminars in Medical Genetics. 127(1):35-41.

(158) Roebuck TM, Mattson SN, Riley EP. A review of the neuroanatomical findings in children with fetal alcohol syndrome or prenatal exposure to alcohol. Alcohol Clin Exp Res 1998; 22(2):339-344.

(159) Roebuck TM, Mattson SN, Riley EP. Behavioral and psychosocial profiles of alcohol-exposed children. Alcohol Clin Exp Res 1999; 23(6):1070-1076.

(160) Streissguth AP, Barr HM, Sampson PD. Moderate prenatal alcohol exposure: effects on child IQ and learning problems at age 7 1/2 years. Alcohol Clin Exp Res 1990; 14(5):662-669.

(161) Streissguth AP. Fetal alcohol syndrome: early and long-term consequences. NIDA Research Monograph 1992; 119:126-130.

(162) Streissguth AP, Sampson PD, Olson HC, Bookstein FL, Barr HM, Scott M et al. Maternal drinking during pregnancy: attention and short-term memory in 14-year-old offspring--a longitudinal prospective study. Alcohol Clin Exp Res 1994; 18(1):202-218.

(163) Swayze VW, Johnson VP, Hanson JW, Piven J, Sato Y, Giedd JN et al. Magnetic resonance imaging of brain anomalies in fetal alcohol syndrome. Pediatrics 1997; 99(2):232-240.

(164) Streissguth AP, Barr HM, Martin DC. Maternal alcohol use and neonatal habituation assessed with the Brazelton scale. Child Development 1983; 54(5):1109-1118.

(165) Gusella JL, Fried PA. Effects of maternal social drinking and smoking on offspring at 13 months. Neurobehav Toxicol Teratol 1984; 6(1):13-17.

(166) Streissguth AP, Herman CS, Smith DW. Intelligence, behavior, and dysmorphogenesis in the fetal alcohol syndrome: a report on 20 patients. J Pediatr 1978; 92(3):363-367.

(167) Streissguth AP, Herman CS, Smith DW. Stability of intelligence in the fetal alcohol syndrome: a preliminary report. Alcohol Clin Exp Res 1978; 2(2):165-170.

(168) Singer LT, Arendt R, Minnes S, Farkas K, Salvator A, Kirchner HL et al. Cognitive and motor outcomes of cocaine-exposed infants. JAMA 2002; 287(15):1952-1960.

(169) Aronson M, Olegard R. Children of alcoholic mothers. Pediatrician 1987; 14(1-2):57-61.

(170) Jacobson SW, Jacobson JL, Sokol RJ, Chiodo LM, Corobana R. Maternal age, alcohol abuse history, and quality of parenting as moderators of the effects of prenatal alcohol exposure on 7.5-year intellectual function. Alcohol Clin Exp Res 2004; 28(11):1732-1745.

(171) Mattson SN, Riley EP. Parent ratings of behavior in children with heavy prenatal alcohol exposure and IQ-matched controls. Alcohol Clin Exp Res 2000; 24(2):226-231.

(172) Sood B, Delaney-Black V, Covington C, Nordstrom-Klee B, Ager J, Templin T et al. Prenatal alcohol exposure and childhood behavior at age 6 to 7 years: I. dose-response effect. Pediatrics 2001; 108(2):E34.

(173) Testa M, Quigley BM, Eiden RD. The effects of prenatal alcohol exposure on infant mental development: a meta-analytical review. Alcohol Alcohol 2003; 38(4):295-304.

(174) Whaley SE, O'Connor And MJ, Gunderson B. Comparison of the adaptive functioning of children prenatally exposed to alcohol to a nonexposed clinical sample. Alcohol Clin Exp Res 2001; 25(7):1018-1024.

(175) Thomas SE, Kelly SJ, Mattson SN, Riley EP. Comparison of social abilities of children with fetal alcohol syndrome to those of children with similar IQ scores and normal controls. Alcohol Clin Exp Res 1998; 22(2):528-533.

(176) Brown RT, Coles CD, Smith IE, Platzman KA, Silverstein J, Erickson S et al. Effects of prenatal alcohol exposure at school age. II. Attention and behavior. Neurotoxicology & Teratology 1991; 13(4):369-376.

(177) Landesman-Dwyer S, Ragozin AS, Little RE. Behavioral correlates of prenatal alcohol exposure: a four-year follow-up study. Neurobehav Toxicol Teratol 1981; 3(2):187-193.

(178) Bingham CR, Shope JT, Tang X. Drinking behavior from high school to young adulthood: differences by college education. Alcohol Clin Exp Res 2005; 29(12):2170-2180.

(179) Ebrahim SH, Decoufle P, Palakathodi AS. Combined tobacco and alcohol use by pregnant and reproductive-aged women in the United States. Obstetrics & Gynecology 2000; 96(5 Pt 1):767-771.

(180) Phares TM, Morrow B, Lansky A, Barfield WD, Prince CB, Marchi KS et al. Surveillance for disparities in maternal health-related behaviors--selected states,

Pregnancy Risk Assessment Monitoring System (PRAMS), 2000-2001. Morbidity & Mortality Weekly Report 2004; Surveillance Summaries. 53(4):1-13.

(181) Prescott CA, Neale MC, Corey LA, Kendler KS. Predictors of problem drinking and alcohol dependence in a population-based sample of female twins. Journal of Studies on Alcohol 1997; 58(2):167-181.

(182) Walker DS, Fisher CS, Sherman A, Wybrecht B, Kyndely K. Fetal alcohol spectrum disorders prevention: an exploratory study of women's use of, attitudes toward, and knowledge about alcohol. J Am Acad Nurse Pract 2005; 17(5):187-193.

(183) Jacobson SW, Carr LG, Croxford J, Sokol RJ, Li TK, Jacobson JL. Protective effects of the alcohol dehydrogenase-ADH1B allele in children exposed to alcohol during pregnancy. J Pediatr 2006; 148(1):30-37.

(184) Jacobson JL, Jacobson SW, Sokol RJ. Increased vulnerability to alcohol-related birth defects in the offspring of mothers over 30. Alcohol Clin Exp Res 1996; 20(2):359-363.

(185) Jacobson JL, Jacobson SW, Sokol RJ, Ager JW, Jr. Relation of maternal age and pattern of pregnancy drinking to functionally significant cognitive deficit in infancy. Alcohol Clin Exp Res 1998; 22(2):345-351.

(186) Jacobson JL, Jacobson SW. Drinking moderately and pregnancy. Effects on child development. Alcohol Res Health 1999; 23(1):25-30.

(187) Robinson GC. Appraisal of the epidemiology of fetal alcohol syndrome among Canadian native peoples. Canadian Journal of Public Health Revue Canadienne de Sante Publique 1989; 80(5):382.

(188) O'Leary CM, Heuzenroeder L, Elliott EJ, Bower C. A review of policies on alcohol use during pregnancy in Australia and other English-speaking countries, 2006. Med J Aust 2007; 186(9):466-471.

(189) Barr HM, Bookstein FL, O'Malley KD, Connor PD, Huggins JE, Streissguth AP. Binge drinking during pregnancy as a predictor of psychiatric disorders on the Structured Clinical Interview for DSM-IV in young adult offspring. American Journal of Psychiatry 2006; 163(6):1061-1065.

(190) Scher MS, Richardson GA, Coble PA, Day NL, Stoffer DS. The effects of prenatal alcohol and marijuana exposure: disturbances in neonatal sleep cycling and arousal. Pediatric Research 1988; 24(1):101-105.

(191) MacGregor SN, Keith LG, Chasnoff IJ, Rosner MA, Chisum GM, Shaw P et al. Cocaine use during pregnancy: adverse perinatal outcome. American Journal of Obstetrics & Gynecology 1987; 157(3):686-690.

(192) Singer LT, Arendt RE. Prenatal cocaine exposure as a risk factor for later developmental outcomes. JAMA 2001; 286(1):45-46.

(193) Wilson GS. Clinical studies of infants and children exposed prenatally to heroin. Annals of the New York Academy of Sciences 1989; 562:183-194.

(194) Singer LT, Hawkins S, Huang J, Davillier M, Baley J. Developmental outcomes and environmental correlates of very low birthweight, cocaine-exposed infants. Early Hum Dev 2001; 64(2):91-103.

(195) Noland JS, Singer LT, Arendt RE, Minnes S, Short EJ, Bearer CF. Executive functioning in preschool-age children prenatally exposed to alcohol, cocaine, and marijuana. Alochol Clin Exp Res 2003; 27(4):647-656.

(196) Clarke M, Hornick J. The development of the Nurturance Inventory: an instrument for assessing parenting practices. Child Psychiatry Hum Dev 1984; 15(1):49-63.

(197) Frankenburg WK, Coons CE. Home Screening Questionnaire: its validity in assessing home environment. J Pediatr 1986; 108(4):624-626.

(198) Jester JM, Jacobson SW, Sokol RJ, Tuttle BS, Jacobson JL. The influence of maternal drinking and drug use on the quality of the home environment of school-aged children. Alcohol Clin Exp Res 2000; 24(8):1187-1197.

(199) Bell R, Lumley J. Alcohol consumption, cigarette smoking and fetal outcome in Victoria, 1985. Community Health Studies 1989; 13(4):484-491.

(200) Lumley J, Correy JF, Newman NM, Curran JT. Cigarette smoking, alcohol consumption and fetal outcome in Tasmania 1981-82. Aust N Z J Obstet Gynaecol 1985; 25(1):33-40.

(201) Walpole I, Zubrick S, Pontre J. Confounding variables in studying the effects of maternal alcohol consumption before and during pregnancy. J Epidemiol Community Health 1989; 43(2):153-161.

(202) Mortensen EL, Michaelsen KF, Sanders SA, Reinisch JM. The association between duration of breastfeeding and adult intelligence. JAMA 2002; 287(18):2365-2371.

(203) Barr HM, Streissguth AP. Caffeine use during pregnancy and child outcome: a 7-year prospective study. Neurotoxicology & Teratology 1991; 13(4):441-448.

(204) Bagheri MM, Burd L, Martsolf JT, Klug MG. Fetal alcohol syndrome: maternal and neonatal characteristics. J Perinat Med 1998; 26(4):263-269.

(205) Noland JS, Singer LT, Mehta SK, Super DM. Prenatal cocaine/polydrug exposure and infant performance on an executive functioning task. Dev Neuropsychol 2003; 24(1):499-517.

(206) O'Callaghan FV, O'Callaghan M, Najman JM, Williams GM, Bor W. Maternal alcohol consumption during pregnancy and physical outcomes up to 5 years of age: A longitudinal study. Early Human Development 2003; 71(2):137-148.

(207) Brown JV, Bakeman R, Coles CD, Sexson WR, Demi AS. Maternal drug use during pregnancy: are preterm and full-term infants affected differently? Dev Psychol 1998; 34(3):540-554.

(208) Kesmodel U, Wisborg K, Olsen SF, Henriksen TB, Secher NJ. Moderate alcohol intake during pregnancy and the risk of stillbirth and death in the first year of life. Am J Epidemiol 2002; 155(4):305-312.

(209) Lundsberg LS, Bracken MB, Saftlas AF. Low-to-moderate gestational alcohol use and intrauterine growth retardation, low birthweight, and preterm delivery. Ann Epidemiol 1997; 7(7):498-508.

(210) Werner EE. Vulnerable but invincible: high-risk children from birth to adulthood. Acta Paediatrica Supplement 1997; 422:103-105.

(211) Little RE, Asker RL, Sampson PD, Renwick JH. Fetal growth and moderate drinking in early pregnancy. Am J Epidemiol 1986; 123(2):270-278.

(212) Kilbride HW, Johnson DL, Streissguth AP. Social class, birth order, and newborn experience. Child Development 1977; 48(4):1686-1688.

(213) Health Canada. Health Canada. Joint statement: prevention of fetal alcohol syndrome (FAS), fetal alcohol effects (FAE) in Canada. 1996.

(214) US Department of Agriculture/US Department of Health and Human Services. Nutrition and your health: dietary guidelines for Americans, 3rd ed. 25-26. 1990. Washington, DC, US Department of Agriculture/US Department of Health and Human Services.

(215) Bearer CF. Markers to Detect Drinking During Pregnancy. Alcohol Res Health 2001; 25(3):210-218.

(216) Health Canada. Perinatal Health Indicators for Canada: A Resource Manual. Cat. No. H49-135/2000E, ISBN 0-662-28850-5. 2000. Ottawa, Minister of Public Works and Government Services Canada.

(217) From the Centers for Disease Control and Prevention. Alcohol use among women of childbearing age--United States, 1991-1999. JAMA 2002; 287(16):2069-2071.

(218) Alcohol consumption among women who are pregnant or who might become pregnant--United States, 2002. MMWR Morb Mortal Wkly Rep 2004; 53(50):1178-1181.

(219) National Institute on Drug Abuse. National household survey on drug abuse: 1988 population estimates. Publication #89-1636. 1989. Washington, DC, US Department of Health and Human Services.

(220) Streissguth AP, Grant TM, Barr HM, Brown ZA, Martin JC, Mayock DE et al. Cocaine and the use of alcohol and other drugs during pregnancy. American Journal of Obstetrics & Gynecology 1991; 164(5:Pt 1):1239-1243.

(221) MacNeil P, Webster I. Canada's alcohol and other drugs survey 1994: A discussion of the findings. 1994. Ottawa, ON, Health Canada.

(222) Flynn HA, Marcus SM, Barry KL, Blow FC. Rates and correlates of alcohol use among pregnant women in obstetrics clinics. Alochol Clin Exp Res 2003; 27(1):81-87.

(223) Marcus SM, Flynn HA, Blow FC, Barry KL. Depressive symptoms among pregnant women screened in obstetrics settings. Journal of Women's Health 2003; 12(4):373-380.

(224) May PA, Gossage P. New data on the epidemiology of adult drinking and substance use among American Indians of the northern states: male and female data on prevalence, patterns, and consequences. American Indian & Alaska Native Mental Health Research (Online) 2001; 10(2):1-26.

(225) May PA, Gossage JP. Estimating the prevalence of fetal alcohol syndrome. A summary. Alcohol Research & Health: the Journal of the National Institute on Alcohol Abuse & Alcoholism 2001; 25(3):159-167.

(226) May PA, Gossage JP, White-Country M, Goodhart K, Decoteau S, Trujillo PM et al. Alcohol consumption and other maternal risk factors for fetal alcohol syndrome among three distinct samples of women before, during, and after pregnancy: the risk is relative. American Journal of Medical Genetics 2004; Part C, Seminars in Medical Genetics. 127(1):10-20.

(227) May PA, Gossage JP, Brooke LE, Snell CL, Marais AS, Hendricks LS et al. Maternal risk factors for fetal alcohol syndrome in the Western cape province of South Africa: a population-based study. American Journal of Public Health 2005; 95(7):1190-1199.

(228) Floyd RL, Decoufle P, Hungerford DW. Alcohol use prior to pregnancy recognition. Am J Prev Med 1999; 17(2):101-107.

(229) Tough S, Tofflemire K, Clarke M, Newburn-Cook C. Do Women Change Their Drinking Behaviors While Trying to Conceive? An Opportunity for Preconception Counseling. Clin Med Res 2006; 4(2):97-105.

(230) Chasnoff IJ, Landress HJ, Barrett ME. The prevalence of illicit-drug or alcohol use during pregnancy and discrepancies in mandatory reporting in Pinellas County, Florida.[comment]. New Engl J Med 1990; 322(17):1202-1206.

(231) Bearer CF. Markers to detect drinking during pregnancy. Alcohol Research & Health: the Journal of the National Institute on Alcohol Abuse & Alcoholism 2001; 25(3):210-218.

(232) Bearer CF, Gould S, Emerson R, Kinnunen P, Cook CS. Fetal alcohol syndrome and fatty acid ethyl esters. Pediatric Research 1992; 31(5):492-495.

(233) Bearer CF, Lee S, Salvator AE, Minnes S, Swick A, Yamashita T et al. Ethyl linoleate in meconium: a biomarker for prenatal ethanol exposure. Alcohol Clin Exp Res 1999; 23(3):487-493.

(234) Bearer CF. Meconium as a biological marker of prenatal exposure. Ambulatory Pediatrics 2003; 3(1):40-43.

(235) Chan D, Bar-Oz B, Pellerin B, Paciorek C, Klein J, Kapur B et al. Population baseline of meconium fatty acid ethyl esters among infants of nondrinking women in Jerusalem and Toronto.[erratum appears in Ther Drug Monit. 2004 Oct;26(5):583]. Ther Drug Monit 2003; 25(3):271-278.

(236) Chan D, Caprara D, Blanchette P, Klein J, Koren G. Recent developments in meconium and hair testing methods for the confirmation of gestational exposures to alcohol and tobacco smoke. Clinical Biochemistry 2004; 37(6):429-438.

(237) Bibb KW, Stewart DL, Walker JR, Cook VD, Wagener RE. Drug screening in newborns and mothers using meconium samples, paired urine samples, and interviews. Journal of Perinatology 1995; 15(3):199-202.

(238) Ostrea EM, Jr., Knapp DK, Tannenbaum L, Ostrea AR, Romero A, Salari V et al. Estimates of illicit drug use during pregnancy by maternal interview, hair analysis, and meconium analysis. J Pediatr 2001; 138(3):344-348.

(239) Laposata M. Fatty acid ethyl esters: short-term and long-term serum markers of ethanol intake. Clinical Chemistry 1997; 43(8 Pt 2):1527-1534.

(240) Derauf C, Katz AR, Easa D. Agreement between maternal self-reported ethanol intake and tobacco use during pregnancy and meconium assays for fatty acid ethyl esters and cotinine. American Journal of Epidemiology 2003; 158(7):705-709.

(241) Kaluzny MA, Duncan LA, Merritt MV, Epps DE. Rapid separation of lipid classes in high yield and purity using bonded phase columns. Journal of Lipid Research 1985; 26(1):135-140.

(242) Clarke DW, Smith GN, Patrick J, Richardson B, Brien JF. Activity of alcohol dehydrogenase and aldehyde dehydrogenase in maternal liver, fetal liver and placenta of the near-term pregnant ewe. Dev Pharmacol Ther 1989; 12(1):35-41.

(243) Laposata M. Fatty acid ethyl esters: nonoxidative ethanol metabolites with emerging biological and clinical significance. [Review] [29 refs]. Lipids 1999; 34 Suppl:S281-S285.

(244) Soderberg BL, Sicinska ET, Blodget E, Cluette-Brown JE, Suter PM, Schuppisser T et al. Preanalytical variables affecting the quantification of fatty acid ethyl esters in plasma and serum samples. Clinical Chemistry 1999; 45(12):2183-2190.

(245) Mac E PMGGea. A marker of fetal exposure to alcohol by meconium analysis. Pediatr Res 35, 238A. 1994.

(246) Bearer CF, Swick A, Singer L. FAEE: biomarker for prenatal alcohol use. Alcohol Clin Exp Res 1996; 20:139A.

(247) Derauf C, Katz AR, Easa D. Agreement between maternal self-reported ethanol intake and tobacco use during pregnancy and meconium assays for fatty acid ethyl esters and cotinine. Am J Epidemiol 2003; 158(7):705-709.

(248) Noland JS, Singer LT, Short EJ, Minnes S, Arendt RE, Kirchner HL et al. Prenatal drug exposure and selective attention in preschoolers. Neurotoxicol Teratol 2005; 27(3):429-438.

(249) Campbell DE, Fleischman AR. Ethical challenges in medical care for the pregnant substance abuser. Clinical Obstetrics & Gynecology 1992; 35(4):803-812.

(250) British Columbia Provincial Perinatal Steering Committee. Substance use guideline 1: Principles of perinatal care for substance using women and their newborns. British Columbia Reproductive Care Program . 1999. 5-6-2003.

(251) British Columbia Provincial Perinatal Steering Committee. Neonatal guideline 9: Newborn screening. British Columbia Reproductive Care Program . 1999. 5-6-2003.

(252) Flagler E, Baylis F, Rodgers S. Bioethics for clinicians: 12. Ethical dilemmas that arise in the care of pregnant women: rethinking "maternal-fetal conflicts". CMAJ Canadian Medical Association Journal 1997; 156(12):1729-1732.

(253) Etchells E, Sharpe G, Walsh P, Williams JR, Singer PA. Bioethics for clinicians: 1. Consent. Canadian Medical Association Journal 1996; 155(2):177-180.

(254) Canadian Charter of Rights and Freedoms. Department of Justice Canada Part I of the Constitution Act 1982, enacted as Schedule B to the Canada Act 1982 (U.K.). 1982. 5-6-2003.

(255) Canadian Medical Association. Code of Ethics. Canadian Medical Association . 2003. 5-6-2003.

(256) Abel EL, Kruger M. Physician attitudes concerning legal coercion of pregnant alcohol and drug abusers. American Journal of Obstetrics & Gynecology 2002; 186(4):768-772.

(257) Crystal M. Ferguson, et al. v. City of Charleston et al. Ferguson v. City of Charleston. [No. 99-936]. 1993. United States Supreme Court. 21-3-2001.

(258) British Columbia Provincial Perinatal Steering Committee. Substance use guideline 5B: Perinatal cocaine exposure, care of the newborn. British Columbia Reproductive Care Program . 1999. 5-6-2003.

(259) British Columbia Provincial Perinatal Steering Committee. Substance use guideline 5A: Perinatal cocaine use, care of the mother. British Columbia Reproductive Care Program . 1999. 5-6-2003.

(260) British Columbia Provincial Perinatal Steering Committee. Substance use guideline 4B: Perinatal opioid exposure, care of the newborn. British Columbia Reproductive Care Program . 1999. 5-6-2003.

(261) British Columbia Provincial Perinatal Steering Committee. Substance use guideline 4A: Perinatal opioid use, care of the mother. British Columbia Reproductive Care Program . 1999. 5-6-2003.

(262) Herek GM, Capitanio JP, Widaman KF. HIV-related stigma and knowledge in the United States: prevalence and trends, 1991-1999. Am J Public Health 2002; 92(3):371-377.

(263) Herek GM, Capitanio JP, Widaman KF. Stigma, social risk, and health policy: public attitudes toward HIV surveillance policies and the social construction of illness. Health Psychol 2003; 22(5):533-540.

(264) Jayaraman GC, Preiksaitis JK, Larke B. Mandatory reporting of HIV infection and opt-out prenatal screening for HIV infection: effect on testing rates. CMAJ 2003; 168(6):679-682.

(265) Tay EG, Emmanuel SC. Improving the uptake of human immunodeficiency virus (HIV) antenatal screening in a primary healthcare setting. Annals of the Academy of Medicine, Singapore 2003; 32(1):92-95.

(266) Health Canada. HIV/AIDS EPI Updates: Perinatal transmission of HIV. 25-30. 2003.

(267) Rutman D, Callahan M, Lundquist A, Jackson S, Field B. Substance use and pregnancy: Conceiving women in the policy-making precess. Policy Research. Ottawa, ON, Status of Women Canada.

(268) Rosenstock IM, Strecher VJ, Becker MH. Social learning theory and the Health Belief Model. Health Education Quarterly 1988; 15(2):175-183.

(269) Salazar MK. Comparison of four behavioral theories. A literature review. AAOHN Journal 1991; 39(3):128-135.

(270) Harrison JA, Mullen PD, Green LW. A meta-analysis of studies of the Health Belief Model with adults. Health Educ Res 1992; 7(1):107-116.

(271) Branco EI, Kaskutas LA. "If it burns going down... ": how focus groups can shape fetal alcohol syndrome (FAS) prevention. Substance Use & Misuse 2001; 36(3):333-345.

(272) Tough SC, Clarke M, Hicks M, Clarren S. Variation in health care provider definitions of moderate consumption of alcohol as related to recommendations regarding alcohol consumption during pregnancy: results from a Canadian survey. Ther Drug Monit 2005; 27(3):290-296.

(273) Tough SC, Clarke M, Hicks M, Cook J. Pre-conception practices among family physicians and obstetrician-gynaecologists: results from a national survey. J Obstet Gynaecol Can 2006; 28(9):780-788.

(274) Harrison JA, Mullen PD, Green LW. A meta-analysis of studies of the Health Belief Model with adults. Health Educ Res 1992; 7(1):107-116.

(275) Brown JB, Lent B, Brett PJ, Sas G, Pederson L. Development of woman abuse screening tool for use in family practice. Family Medicine 1996; 28(6):422-428.

(276) Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987; 150:782-786.

(277) Kellner R. A symptom questionnaire. J Clin Psychiatry 1987; 48(7):268-274.

(278) McCubbin HI, Patterson J, Glynn T. Social support index (SSI) (1982). In: Corcoran K, Fischer J, editors. Measures for Clinical Practice: A Sourcebook. New York: Free Press, 2000: 446-447.

(279) McCubbin HI, Patterson J, Glynn T. Measures for clinical practice: a sourcebook. In: Corcoran K, Fischer J, editors. 2000.

(280) Rosenberg M. Society and the Adolescent Self-Image. Princeton, NJ: Princeton University Press, 1965.

(281) Rosenberg MJ. Society and the Adolescent Self-Image. Revised ed. Middletown, CT: Wesleyan University Press, 1989.

(282) Vaux AC, Burda PC, Stewart D. Orientation toward utilization of support resources. J Community Psychol 1986; 14(2):159-170.

(283) Tambay J, Catlin G. Sample design of the National Population Health Survey. Health Reports 1995; 7:1-11.

(284) SPSS for Windows, Rel 14.01. Chicago, Illinois: SPSS Inc., 2006.

(285) Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. Clin Chem 2003; 49(1):7-18.

(286) Rennie D. Improving reports of studies of diagnostic tests: the STARD initiative. JAMA 2003; 289(1):89-90.

(287) Stata Corporation. Stata Reference Manual Extract Release 9. College Station, Stata Press.

(288) Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. Pediatrics 2002; 109(1):45-60.

(289) Bayley N. Bayley Scales of Infant Development. 2 ed. San Antonio: The Psychological Corporation, 1993.

(290) Achenbach TM, Rescorla LA. Manual for ASEBA Preschool Forms & Profiles. 2000. Burlington, VT, University of Vermont, Research Center for Children, Youth & Families.

(291) Bagnato SJ, Neisworth JT, Salvia JJ, Hunt FM. Temperament and Atypical Behavior Scale (TABS). Early Childhood Indicators of Developmental Dysfunction. 1999. Baltimore, MD, Paul H. Brookes Publishing Co.

(292) Fullard W, McDevitt SC, Carey WB. Assessing temperament in one- to three-year-old children. Journal of Pediatric Psychology 1984; 9(2):205-217.

(293) Hubert NC, Wachs T, Peters-Martin P, Gandour MJ. The study of early temperament: Measurement and conceptual issues. Child Development 571; 53(3):US.

(294) Guidubaldi J, Cleminshaw HK. Parenting Satisfaction Scale Manual. 1997. San Antonio, The Psychological Corporation.

(295) The Psychological Corporation. Wechsler Abbreviated Scale of Intelligence Manual. 1997. San Antonio, Texas, PsychCorp, Harcourt Assessments, Inc.

(296) Epstein NB, Baldwin LM, Bishop DS. The McMaster Family Assessment Device. Journal of Maternal-Fetal & Neonatal Medicine 1983; 9(2):171-180.

(297) Miller IW, Epstein NB, Bishop DS, Keitner GI. The McMaster Family Assessment Device: reliability and validity. Journal of Marital and Family Therapy 1985; 11(4):345-356.

(298) Streissguth AP, Guinta CT. Subject recruitment and retention for longitudinal research: practical considerations for a nonintervention model. NIDA Research Monograph 1992; 117:137-154.

(299) Statistics Canada. Calgary Health Region Demographics. Statistics Canada . 2005. 1-2-2005.

(300) Marcus SM, Flynn HA, Blow FC, Barry KL. Depressive symptoms among pregnant women screened in obstetrics settings.[see comment]. Journal of Women's Health 2003; 12(4):373-380.

(301) Autti-Ramo I, Fagerlund A, Ervalahti N, Loimu L, Korkman M, Hoyme HE. Fetal alcohol spectrum disorders in Finland: clinical delineation of 77 older children and adolescents. Am J Med Genet A 2006; 140(2):137-143.

(302) Salem RO, Cluette-Brown JE, Laposata M. Fatty acid ethyl esters, nonoxidative ethanol metabolites, synthesis, uptake, and hydrolysis by human platelets. Biochim Biophys Acta 2005; 1738(1-3):99-104.

(303) Saghir M, Blodget E, Laposata M. The hydrolysis of fatty acid ethyl esters in low-density lipoproteins by red blood cells, white blood cells and platelets. Alcohol 1999; 19(2):163-168.

(304) Dahshan A, Donovan K. Auto-brewery syndrome in a child with short gut syndrome: case report and review of the literature. J Pediatr Gastroenterol Nutr 2001; 33(2):214-215.

(305) Logan BK, Jones AW. Endogenous ethanol production in a child with short gut syndrome. J Pediatr Gastroenterol Nutr 2003; 36(3):419-420.

(306) Jansson-Nettelbladt E, Meurling S, Petrini B, Sjolin J. Endogenous ethanol fermentation in a child with short bowel syndrome. Acta Paediatr 2006; 95(4):502-504.

(307) Logan BK, Jones AW. Endogenous ethanol 'auto-brewery syndrome' as a drunk-driving defence challenge. Med Sci Law 2000; 40(3):206-215.

(308) Roberts G, Nanson JL. Best Practices: Fetal Alcohol Syndrome/Fetal Alcohol Effects and the Effects of Other Substance Use During Pregnancy. 2000. Health Canada.

(309) McNamara TK, Orav EJ, Wilkins-Haug L, Chang G. Social support and prenatal alcohol use. Journal of Women's Health 2006; 15(1):70-76.

(310) Chang G, Goetz MA, Wilkins-Haug L, Berman S. A brief intervention for prenatal alcohol use: an in-depth look. J Subst Abuse Treat 2000; 18(4):365-369.

(311) Chang G, McNamara TK, Orav EJ, Koby D, Lavigne A, Ludman B et al. Brief intervention for prenatal alcohol use: a randomized trial. Obstetrics & Gynecology 2005; 105(5 Pt 1):991-998.

(312) Grant TM, Ernst CC, Streissguth AP. An intervention with high-risk mothers who abuse alcohol and drugs: the Seattle Advocacy Model. American Journal of Public Health 1996; 86(12):1816-1817.

(313) Wutzke SE, Conigrave KM, Saunders JB, Hall WD. The long-term effectiveness of brief interventions for unsafe alcohol consumption: a 10-year follow-up. Addiction 2002; 97(6):665-675.

(314) Abel EL. Maternal alcohol consumption and spontaneous abortion. [Review] [45 refs]. Alcohol & Alcoholism 1997; 32(3):211-219.

(315) Kalberg WO, Provost B, Tollison SJ, Tabachnick BG, Robinson LK, Eugene HH et al. Comparison of motor delays in young children with fetal alcohol

syndrome to those with prenatal alcohol exposure and with no prenatal alcohol exposure. Alcohol Clin Exp Res 2006; 30(12):2037-2045.

(316) Kaplan-Estrin M, Jacobson SW, Jacobson JL. Neurobehavioral effects of prenatal alcohol exposure at 26 months. Neurotoxicol Teratol 1999; 21(5):503-511.

(317) Roebuck TM, Simmons RW, Richardson C, Mattson SN, Riley EP. Neuromuscular responses to disturbance of balance in children with prenatal exposure to alcohol. Alcohol Clin Exp Res 1998; 22(9):1992-1997.

(318) Connor PD, Sampson PD, Streissguth AP, Bookstein FL, Barr HM. Effects of prenatal alcohol exposure on fine motor coordination and balance: A study of two adult samples. Neuropsychologia 2006; 44(5):744-751.

(319) Bailey BN, Delaney-Black V, Covington CY, Ager J, Janisse J, Hannigan JH et al. Prenatal exposure to binge drinking and cognitive and behavioral outcomes at age 7 years. Am J Obstet Gynecol 2004; 191(3):1037-1043.

(320) Brien JF, Chan D, Green CR, Iqbal U, Gareri J, Kobus SM et al. Chronic prenatal ethanol exposure and increased concentration of fatty acid ethyl esters in meconium of term fetal Guinea pig. Ther Drug Monit 2006; 28(3):345-350.

(321) Jacobson SW, Chiodo LM, Sokol RJ, Jacobson JL. Validity of maternal report of prenatal alcohol, cocaine, and smoking in relation to neurobehavioral outcome. Pediatrics 2002; 109(5):815-825.

(322) Young C, Olney JW. Neuroapoptosis in the infant mouse brain triggered by a transient small increase in blood alcohol concentration. Neurobiol Dis 2006; 22(3):548-554.

(323) Redila VA, Olson AK, Swann SE, Mohades G, Webber AJ, Weinberg J et al. Hippocampal cell proliferation is reduced following prenatal ethanol exposure but can be rescued with voluntary exercise. Hippocampus 2006; 16(3):305-311.

(324) Olson AK, Eadie BD, Ernst C, Christie BR. Environmental enrichment and voluntary exercise massively increase neurogenesis in the adult hippocampus via dissociable pathways. Hippocampus 2006; 16(3):250-260.

(325) Christie BR, Swann SE, Fox CJ, Froc D, Lieblich SE, Redila V et al. Voluntary exercise rescues deficits in spatial memory and long-term potentiation in prenatal ethanol-exposed male rats. Eur J Neurosci 2005; 21(6):1719-1726.

(326) Eadie BD, Redila VA, Christie BR. Voluntary exercise alters the cytoarchitecture of the adult dentate gyrus by increasing cellular proliferation, dendritic complexity, and spine density. J Comp Neurol 2005; 486(1):39-47.

(327) Hannigan JH, O'leary-Moore SK, Berman RF. Postnatal environmental or experiential amelioration of neurobehavioral effects of perinatal alcohol exposure in rats. Neurosci Biobehav Rev 2007; 31(2):202-211.

(328) Herek GM, Capitanio JP, Widaman KF. HIV-related stigma and knowledge in the United States: prevalence and trends, 1991-1999. Am J Public Health 2002; 92(3):371-377.

(329) Branson BM, Handsfield HH, Lampe MA, Janssen RS, Taylor AW, Lyss SB et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep 2006; 55(RR-14):1-17.

(330) Ingersoll KS, Lu IL, Haller DL. Predictors of in-treatment relapse in perinatal substance abusers and impact on treatment retention: a prospective study. J Psychoactive Drugs 1995; 27(4):375-387.

(331) Ingersoll K, Floyd L, Sobell M, Velasquez MM. Reducing the risk of alcohol-exposed pregnancies: a study of a motivational intervention in community settings. Pediatrics 2003; 111(5 Part 2):1131-1135.

(332) Ondersma SJ, Malcoe LH, Simpson SM. Child protective services' response to prenatal drug exposure: results from a nationwide survey. Child Abuse & Neglect 2001; 25(5):657-668.

(333) Tough S, Clarke M, Cook J. Fetal Alcohol Spectrum Disorder Prevention Approaches among Canadian Physicians by Proportion of Native/Aboriginal Patients: Practices during the Preconception and Prenatal Periods. Matern Child Health J 2007; 11(4):385-393.

(334) Tough SC, Clarke M, Clarren S. Preventing fetal alcohol spectrum disorders. Preconception counseling and diagnosis help. Can Fam Physician 2005; 51:1199-201.:1199-1201.

(335) Russell T, Crawford M, Woodby L. Measurements for active cigarette smoke exposure in prevalence and cessation studies: why simply asking pregnant women isn't enough. Nicotine Tob Res 2004; 6 Suppl 2:S141-51.:S141-S151.

(336) Alberta Reproductive Health: Pregnancies and Births, 2002. 2002. Edmonton, Alberta, Communications, Alberta Health and Wellness.

(337) US Department of Health and Human Services. *Women and Smoking: A Report of the Surgeon General*. 2001. Rockville, MD, US Department of Health and Human Services, Public Health Service, Office of the Surgeon General.

(338) Wechsler H, Dowdall GW, Maenner G, Gledhill-Hoyt J, Lee H. Changes in binge drinking and related problems among American college students between 1993 and 1997. Results of the Harvard School of Public Health College Alcohol Study. J Am Coll Health 1998; 47(2):57-68.

(339) Wechsler H, Davenport AE, Dowdall GW, Grossman SJ, Zanakos SI. Binge drinking, tobacco, and illicit drug use and involvement in college athletics. A survey of students at 140 American colleges. J Am Coll Health 1997; 45(5):195-200.

(340) Wechsler H, Dowdall GW, Davenport A, Castillo S. Correlates of college student binge drinking. Am J Public Health 1995; 85(7):921-926.

(341) Wechsler H, Davenport A, Dowdall G, Moeykens B, Castillo S. Health and behavioral consequences of binge drinking in college. A national survey of students at 140 campuses. JAMA 1994; 272(21):1672-1677.

(342) Belenky MF, Clinchy BM, Goldberger NR, Tarule JM. Women's ways of knowing: The development of self, voice and mind. Tenth anniversary edition. New York: Basic Books, 1997.

APPENDIX A: TEAM MEMBERS, ETHICAL APPROVAL AND CONSENT FORMS

A.1. Association between Maternal Self-Report of Drug and Alcohol Use and Biomarker in Meconium

A.1.1. Meconium Alcohol and Drug Screening Study Team

Meconium Alcohol and Drug Screening Study Team,
University of Calgary and Calgary Health Region
Core Research Group - Principle investigators, Co-investigators, and Associates

(PI) Suzanne C. Tough, Ph.D.	Community Health Sciences and Paediatrics, Univ. Calgary.
Andrew W. Lyon Ph.D, FCACB	Dept. Pathology and Laboratory Medicine, Univ. Calgary and Calgary Laboratory Services.
Matt Hicks, MD Student/PhD Candidate	Community Health Sciences, Univ. of Calgary
Reg Sauve, MD, MPH, FRCPC	Paediatrics and Community Health Sciences, Univ. of Calgary
Ben Gibbard, MD, MCS, FRCPC	Paediatrics, Univ. of Calgary
Margaret Clarke, MD, FRCPC	Paediatrics, Univ. of Calgary, Fetal Alcohol Syndrome Clinic
Sterling Clarren, MD	Paediatrics, University of Washington
Rollin Brant, PhD	Statistics, University of British Columbia
Dianne Creighton, PhD	Alberta Children's Hospital, Calgary Health Region

Collaborators

CPC Study Group	
Karen Benzies, RN, Ph.D.	Faculty of Nursing, Univ. Calgary.
Laurie Blahitka	Director, Women's Health, Calgary Health Region
Corine Frick, RN,	Director, Inpatient Programs for Children, Calgary Health Region
Bonnie Johnston, CEO,	Calgary Rocky View Child and Family Services
Fay Hodson M.Sc.	Calgary Rocky View Child and Family Services
Shirley Wormsbecker	Fetal Alcohol Syndrome Clinic, Calgary Health Region
Karen McGeary	Manager, Best Beginning, Calgary Health Region
Dena Berci	Calgary Health Region
Valerie Simon	Calgary Laboratory Services
Nalini Singhal, MD, FRCPC;	Paediatrics, Univ. Calgary
Sandra Young, RN, MN	Neonatal Nurse Practitioner, Calgary Health Region
Ian Mitchell, MD, FRCPC	Paediatrics and Office of Bioethics, Univ. of Calgary
Shahirose Premji, RN, Ph.D.	Assistant Professor and Neonatal Nurse Practitioner, University of Calgary and Calgary Health Region
Stacey Dalgleish, RNC, MN	Neonatal Nurse Practitioner, Calgary Health Region
David Johnston, MSc	Decision Support Team, Calgary Health Region`

A.1.2. Proposal Approval by Supervisory Committee (Scientific Review)

UNIVERSITY OF CALGARY

FACULTY OF MEDICINE
Department of Community Health Sciences
Heritage Medical Research Building
Telephone: (403) 220-4294

TO: Dr. R.S. Sauve, Graduate Program Coordinator
Department of Community Health Sciences

DATE: 5 November 2002

FROM: Dr. R.S. Sauve, Professor
Department of Community Health Sciences

RE: **APPROVAL OF PROPOSAL**

Name of Student: **Mr. Matthew Hicks**
Degree Program: **PhD**
Title of Thesis Proposal: **Meconium Alcohol and Drug Screening**

We, the undersigned, have approved the attached proposal and believe that ethical approval should be granted. We acknowledge that if alterations to this proposal are made, we will submit another approval form. This project does not involve the handling of animals.

Dr. R.S. Sauve, Supervisor — Date

Dr. Suzanne Tough
Department of Community Health Sciences — Date

Dr. Margaret Clarke
Department of Paediatrics — Date

Dr. Rollin Brant
Department of Community Health Sciences — Date

Dr. Andrew Lyon
Department of Pathology — Date

cc: Mr. Matthew Hicks
Dr. R.S. Sauve, Acting Head, Department of Community Health Sciences

A.1.3. Ethics Approval for the Community Perinatal Care Study

APR-05-2001 17:30 U OF C OFF. MED BIOETHICS 403 283 8524 P.01/01

UNIVERSITY OF CALGARY

FACULTY OF MEDICINE

Office of Medical Bioethics
Heritage Medical Research Building/Rm 93
Telephone: (403) 220-7990
Fax: (403) 283-8524

2001-04-05

Dr. S. Tough
Department of Paediatrics
Room 413, North Tower
Foothills Hospital
Calgary, Alberta.

Dear Dr. Tough:

Re: Notification of Pregnancy Pilot Project

The above-named research project and the consent forms have been granted ethical approval by the Conjoint Health Research Ethics Board (CHREB) of the Faculties of Medicine, Nursing and Kinesiology, University of Calgary, and the Affiliated Teaching Institutions. The Board conforms to the Tri-Council Guidelines and ICH Guidelines, including membership and requirements for a quorum.

You and your co-investigators are not members of the CHREB and did not participate in review or voting on this study.

Please note that this approval is subject to the following conditions:

(1) you must obtain approval from your appropriate institution where the research project will be conducted (if applicable);
(2) a copy of the informed consent form must have been given to each research subject, if required for this study;
(3) a Progress Report must be submitted in one year, 2002-04-05, containing the following information:
  (i) the number of subjects recruited;
  (ii) a description of any protocol modification;
  (iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
  (iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
  (v) a copy of the current informed consent form;
  (vi) the expected date of termination of this project;
(4) a Final Report must be submitted at the termination of the project.

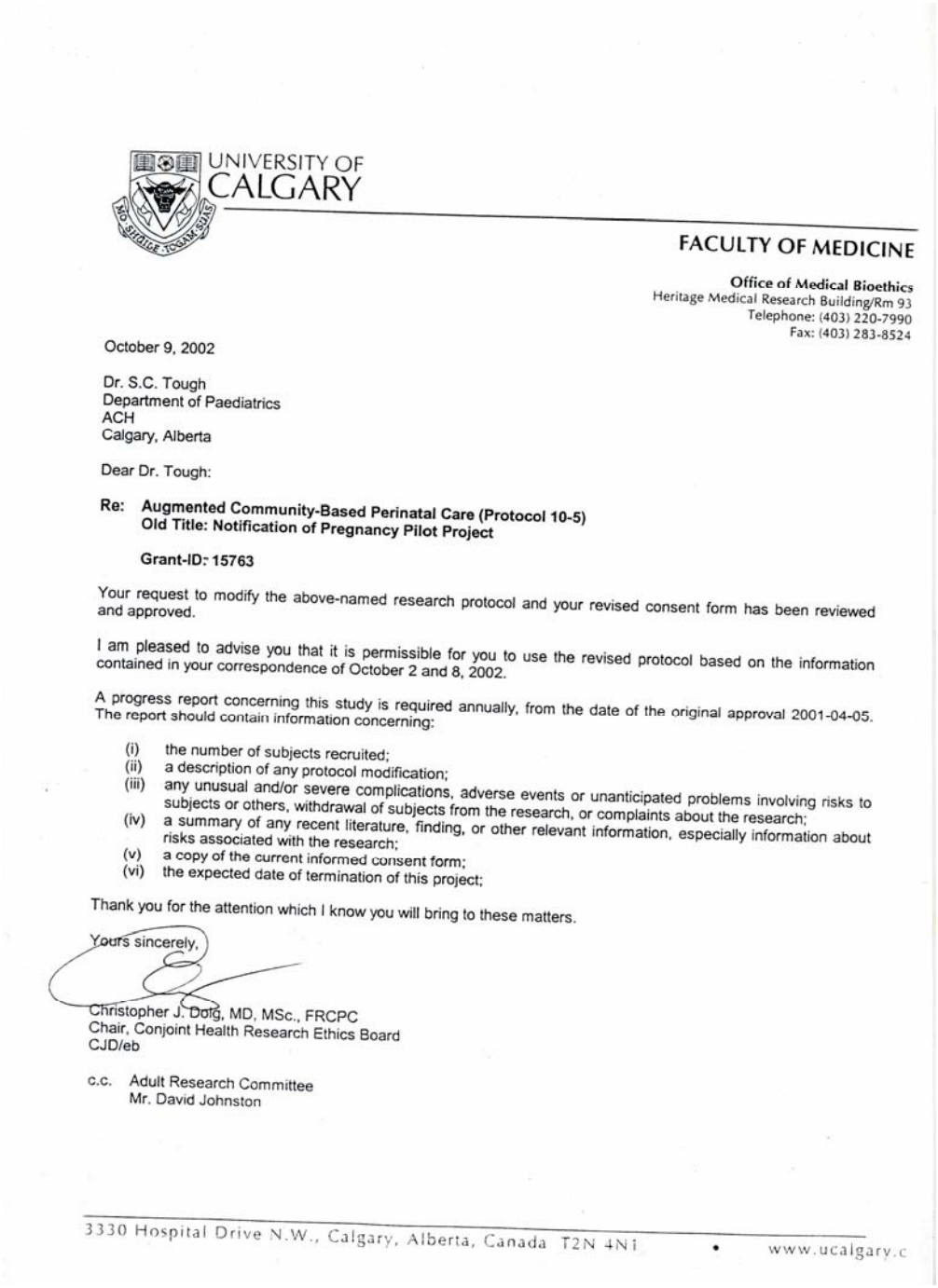
Please accept the Board's best wishes for success in your research.

Yours sincerely,

Christopher J. Doig, MD, MSc, FRCPC
Chair, Conjoint Health Research Ethics Board

c.c. Adult Research Committee
Dr. B. Scott (information)

A.1.4. Ethics Approval for Meconium Screening Study as a Modification of the Community Perinatal Care Study



UNIVERSITY OF CALGARY

FACULTY OF MEDICINE

Office of Medical Bioethics
Heritage Medical Research Building/Rm 93
Telephone: (403) 220-7990
Fax: (403) 283-8524

October 9, 2002

Dr. S.C. Tough
Department of Paediatrics
ACH
Calgary, Alberta

Dear Dr. Tough:

Re: Augmented Community-Based Perinatal Care (Protocol 10-5)
Old Title: Notification of Pregnancy Pilot Project

Grant-ID: 15763

Your request to modify the above-named research protocol and your revised consent form has been reviewed and approved.

I am pleased to advise you that it is permissible for you to use the revised protocol based on the information contained in your correspondence of October 2 and 8, 2002.

A progress report concerning this study is required annually, from the date of the original approval 2001-04-05. The report should contain information concerning:

(i) the number of subjects recruited;
(ii) a description of any protocol modification;
(iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
(iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
(v) a copy of the current informed consent form;
(vi) the expected date of termination of this project;

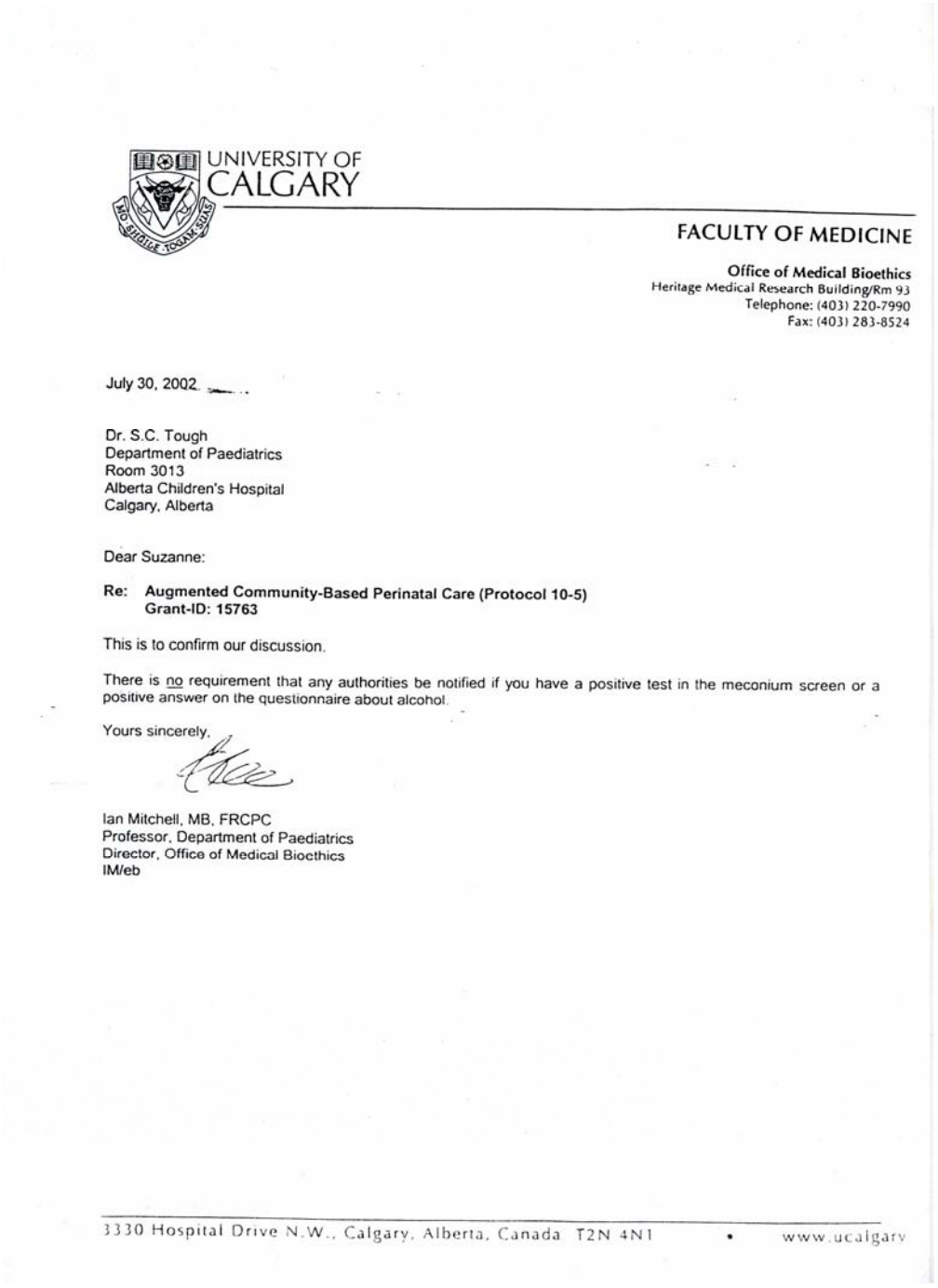
Thank you for the attention which I know you will bring to these matters.

Yours sincerely,

Christopher J. Doig, MD, MSc., FRCPC
Chair, Conjoint Health Research Ethics Board
CJD/eb

c.c. Adult Research Committee
Mr. David Johnston

A.1.5. Confirmation from Ethics that No Authorities Need to be Notified in the Event of a Positive Meconium Screen or for Maternal Report in the Meconium Screening Study



UNIVERSITY OF CALGARY

FACULTY OF MEDICINE

Office of Medical Bioethics
Heritage Medical Research Building/Rm 93
Telephone: (403) 220-7990
Fax: (403) 283-8524

July 30, 2002

Dr. S.C. Tough
Department of Paediatrics
Room 3013
Alberta Children's Hospital
Calgary, Alberta

Dear Suzanne:

Re: Augmented Community-Based Perinatal Care (Protocol 10-5)
Grant-ID: 15763

This is to confirm our discussion.

There is no requirement that any authorities be notified if you have a positive test in the meconium screen or a positive answer on the questionnaire about alcohol.

Yours sincerely,

Ian Mitchell, MB, FRCPC
Professor, Department of Paediatrics
Director, Office of Medical Bioethics
IM/eb

3330 Hospital Drive N.W., Calgary, Alberta, Canada T2N 4N1 • www.ucalgary

A.1.6. Recruitment Forms: Association between Maternal Report and Level of Biomarker

STUDY CONSENT FORM –PARTICIPANT'S COPY (Please keep for your records)
Study Title: Community Perinatal Care Study – **Meconium Screening Substudy**
Principal Investigator: S Tough
Co Investigators: M Hicks, R Sauve, A Lyon, S Premji, S Young, D Johnston, S Dagleish
Sponsor: Alberta Children's Services

We would like to invite you to participate in a project related to mother and child health. The study involves the collection of a sample from your baby's diaper in hospital and 2 questionnaires that will be done over the telephone. The benefit of participating in this study is that you will assist us in assessing methods to improve child health. Results from this study will help us design and offer programs that are specifically targeted to improving pregnancy outcomes and enhancing infant and family health. **Do you have a moment so I could explain more about this project?**

This consent form, a copy of which will be given to you is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

1. Approximately 20% of women in Canada use alcohol during pregnancy and 15% use drugs during pregnancy. The impact of this alcohol and drug use on infant and child health is not well understood. **The purpose of this project is to see if a laboratory test can help us determine what a baby was exposed to during pregnancy.** This lab test involves us collecting meconium, which is your baby's first bowel movements, from your babies diaper. We will then test the meconium for markers for alcohol, cocaine (e.g., crack), opiates (e.g., heroin, morphine, codeine), amphetamines (e.g., speed, crank), cannabinoids (e.g., THC, marijuana, pot, hash, hash oil, weed), and phencyclidine (e.g., PCP, angel dust). We are interested in positive and negative samples.

2. We would also like to ask you questions in two telephone interview about your diet and lifestyle during pregnancy and we would then link the results of the laboratory tests of the meconium to what you told us in the questionnaires. The timing of the questionnaires will be (1) 1 to 2 weeks after you first agree to participate; and (2) two-months after your baby is born. The interviews will take about 30-45 minutes to complete. We will ask you questions about you (e.g. education, marital status), as well as about your medical history, family, lifestyle, and use of community resources. All information you make available to us is confidential and will be used exclusively for study purposes. The information you provide in the questionnaires **will not** be made available to your medical doctor

3. We are also interested in the health of your baby and the care you receive through your medical doctor at the clinic. We ask that you allow us access to the obstetrical records for this pregnancy and the neonatal records for your babies when the time comes.

4. This project does not involve any medical procedures. Your infant's meconium will be collected and sent to a laboratory for analysis. All information will be kept private and confidential. Only study team members will have access to the results of the analysis.

5. There are no short or long term risks associated with collection of the meconium sample. The procedure involves collection of the baby's diaper containing the baby's first bowel

movements. The only inconvenience of participation is related to the time involved.

6. Following delivery your infant will be diapered. At that time a liner will be placed in the diaper to aid in the collection of your infant's first stool.
7. If your infant does not produce a stool prior to hospital discharge then you will be asked to collect the sample at home using a kit that we will provide. We can then arrange to pick the sample up from you.

8. The sample will be identified by the study identification number that we assign to you in this study. The meconium analysis results will be linked to the information you provide us from the questionnaires. This information will not become part of you or your infant's medical record. Only the study team members will have access to the results of meconium analysis. Prior to analysis, any variables that identify you will be removed from the data set. Only the principal investigators or their delegates will be able to link results of laboratory findings to the study data base. The information you provide will be stored in a secured data base with access limited only to the study team. Names will not be used when the information is published. The study data will be kept for at least five years after the study has been completed in a secure area accessible by only the research team. If any further analysis is conducted with the study, further ethics approval will be sought first.

9. If you feel you need medical treatment, or have questions about medical issues, please direct these questions to your medical doctor.

10. At any time you can discontinue participation and if a sample has been collected it will be destroyed.

11. It is anticipated that you will incur no financial costs by participating in this study.

12. In the event that you suffer injury as a result of participating in this research no compensation will be provided for you by the principal investigators, the University of Calgary, or the Calgary Health Region. You still have all your legal rights. Nothing said here about treatment or compensation in any way alters your right to recover damages.

Study Consent

Your written agreement indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time without jeopardizing your health care. Your continued participation should be as informed as your initial consent, so you should feel free to ask for clarification or new information throughout your participation.

_____	_____
Name of Participant (please print)	Signature of Participant
_____	_____
Name of Witness (please print)	Signature of Witness
_____	_____
Signature of Investigator/Study Delegate	Date/Time

A copy of this form will be provided to you for your records.

If you have further questions concerning matters related to this research, please contact:

Matt Hicks	Dr. Suzanne Tough	Dr. Andrew Lyon
Study Coordinator	Project Investigator	Project Investigator
University of Calgary	University of Calgary	University of Calgary
Phone: (403) 943-7539	Phone: (403) 943-2772	Phone: (403) 209-5205

If you have any questions concerning your rights as a possible participant in this research, please contact Pat Evans, Associate Director, Internal Awards, Research Services, University of Calgary, at 220-3782.

Do you consent to participate in the Meconium Screening Study? This will involve the collection and analysis of your infant's first stool.

Participant **Yes** **No**

Are you willing to be contacted for additional research?

Yes **No**

We will be seeing a number of the infants of mothers who participate in this study for long-term developmental follow-up. Children who participate will see a developmental pediatrician to determine if they are developing appropriately. Would you be willing to be approached to participate in this study at a later date?

Yes **No**

We would like to provide you with a study package with information about the study, a card that you will use to identify yourself as a study participant in the hospital, and the sample collection kit that we would like to ask you to bring to the hospital. Please place the study package in your hospital bag when you get home today. Thank you.

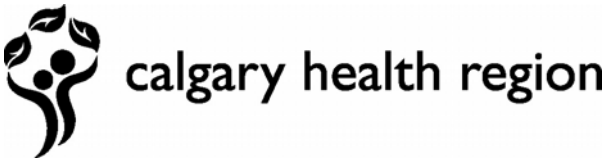
All women in this study continue to see their regular doctors and nurses. **No woman who participates in this study, or her baby, will receive any less medical or community care than they would have received if they had not participated in the study.** You should discuss any medical concerns or questions you have with your regular doctors and nurses. **If you are concerned about possible effects of drug or alcohol exposure on your fetus you could speak with your physician, a public health nurse, or Motherisk at 1-877-327-4636 - for information about the fetal effects of alcohol, nicotine and drugs like marijuana, cocaine and ecstasy.**

At any time you can obtain emotional support through contacting the Crisis Line at (403) 266-1605, or the Calgary Counselling Centre at (403) 265-4980, the Perinatal Bereavement Counselling Centre at (403) 670-2248 or Caring Beyond (403) 294-1131.

Do you have any questions?

I would just like to remind you that all of the information you provide is private and confidential and will only be available to the study team. You can withdraw from the study at any time.

-- This study is funded by Alberta Children's Services



Date of Enrolment:

Community Perinatal Care: Meconium Screening Sub-study
I. COMPLETED FOR ALL NEW Subjects (completed prior to phone call)

1. Patient's name: _____

2. Patient's home phone: _____ Work phone: _____

4. Clinic
   [2] NW, Low Risk Maternity Clinic (Lane, O'Beirne, Spence, Malm, Wilson)
   [3] NW, Maternal Child Clinic (Slocombe, Kingston, Goldie, Kozma, Brown)

We would also like to ask for you address so that we can send you follow up correspondence. What is your address please?

Street_____
_____
City_____
_____
Postal Code_____

May we call you in approximately one to two weeks to go through the first telephone questionnaire?
Yes **No**

5. Date for enrollment questionnaire: ___month ____day _____year
6. Time of day? Morning Afternoon Evening

We would like to confirm your expected due date. Your due date is:_____

For gestational age: _____month _____day _____year [___LMP ___EDC]

Your planned birth hospital is:_____

II. COMPLETED FOR ALL ELIGIBLE SUBJECTS (by Research Assistant)
6. Date of follow up call: ____month ____day _____year

7. Check a box every time try to reach patient under appropriate time (i.e. to assess participation):

8am-6pm □

7pm-9pm □

III. COMPLETED FOR PATIENTS WHO AGREE TO PARTICIPATE (by Research Assistant)

11. Contact if cannot reach this participant: _____ (name) _____(phone)

12. Participant's date of birth: ____month ____day ____year

13. At recruitment date (calculate): Gestational age: ___wks Due Date: ___month ___day _____year

RECORD OF PATIENT TRACKING (completed for patients who agree to participate)

1. Date of Enrollment Interview: ___month ____day _____year

2. Date of first questionnaire: ___month ____day _____year

PATIENT SIGN OFF (completed only for patients who complete first interview)

1. Date Patient Stopped (or completed) Study: ___month ____day _____year

2. Reason patient stopped study:
_____

**********CHECKLIST (initial after completed)**********

(1) info sheet completed by study interviewer __ (2) participation determined __ (3) responses entered in spreadsheet ___ (4) enrollment package mailed to subject ____

COMMUNITY PERINATAL CARE STUDY—MECONIUM SCREENING SUBSTUDY
ANSWERS TO QUESTIONS OR ISSUES THAT INTERVIEWERS MAY EXPERIENCE

1. **How did you get my name?** The [prenatal clinic] is part of the CPC study. We call who are participating in the CPC study and who meet certain eligibility requirements. Eligibility requirements include language, living in Calgary, and responses to alcohol screening questionnaires on the first CPC survey. We realize the pregnancy is a private matter, and to ensure patient confidentiality, we make sure we only talk to the women themselves when calling, and make sure it is a convenient time for them to talk. The study has been approved by the Conjoint Health Research Ethics Board of the University of Calgary.

2. **What if I change my mind about participating? What if I want to drop out?** You can drop out of the study at any time.

3. **Why are you conducting this study/what do you hope to find?** In this study, we have many goals and questions. The main thing we are looking is to determine what sorts of care models work best for women during pregnancy. We are also very interested in the impacts of the different models of service on the prenatal clinic staff.

4. **Can I sign up later?** We allow people a little time to think about whether or not they would like to participate, but people cannot sign up for the study once they have given birth. Ideally we want people to sign up as early as possible, however, we can enroll people as late as 3 weeks before their due date.

5. **I have a friend who might want to be in this study** Only women who are participants in the CPC study are eligible for this study. There are additional eligibility requirements that people must meet.

6. **How do I know you are who you say you are?** That is a very good question. If you would like, I can give you the name of my supervisor. I can also give you the number for the [prenatal clinic] and you could call them to confirm. I can also give you the phone number for the University of Calgary's ethics board, who could answer this question.

7. **Why can't I participate if I am under 18 years old?** This was the recommendation of the conjoint medical research ethics board when this study was approved.

Meconium Screening Specific Questions

8. **Who can see the screening results?** All results of screening analysis are confidential. Screening results cannot be connected to individual babies or mothers.

9. **Why are you doing this study?** We want to determine if meconium screening can reliably identify infants who are at risk for developmental problems. If infants are

identified at a young age then extra education and support can be provided to help minimize any problems.

10. **Will I find out if my infant is at risk?** We will not be releasing individual results of screening analysis to mothers as it is unclear what specific results mean. A general summary of study results will be sent to all study participants. In addition, there is a follow-up component of this study that will look at child development at several points in time for infants with "positive" screens versus "negative" screens. If you have any concerns about any substance that your fetus may have been exposed to then please discuss this with your physician. You can also call Motherisk at **Motherisk at 1-877-327-4636 - for information about the fetal effects of alcohol, nicotine and drugs like marijuana, cocaine and ecstasy.**

If there are indications during follow-up studies that an infant may need assistance or support in reaching developmental goals then examining physicians will recommend that. Such recommendations would be made regardless of meconium screening results or responses on questionnaires.

11. **What happens if I'm taking cough syrup, tylenol with codeine, or cold medication?** We aren't able to predict study results. However, study members are experts in interpreting analyses of these sort. Some substances may interfere with study results and yield a false positive result, that is a positive test result when the true test result should really be negative.

12. **What if I forget the kit and study card?** Spare kits are kept at the hospital. If you identify yourself as a study participant the nurses will be able to collect your sample with a spare kit.

13. **Do you think I'm lying about drug and alcohol use? Is that why you are testing?** This study is not meant to identify subjects on an individual basis. We are examining results based on groups identified from the first CPC questionnaire. This study is about determining if the meconium screening methods can be used as a tool to identify infants at risk. However, no infants will be identified in this study.

Key Contact Numbers

1. David Johnston: 944-4371 (will change to 944-2552 sometime in June)
2. Suzanne Tough: 943-2272
3. Maternal Child Clinic (NW): 289-9051 (office manager=Linda)
   - docs=Sue Kingston, Morag Goldie, Stephanie Kozma, Elwyn Brown, Linda Slocombe
4. Low Risk Maternity Clinic (NW): 509-3080 (receptionist=Kay)
   -docs=M. Obeirne, Norma Spence, Carolyn Lane, S. Malm, Wilson
5. Maternity Care Clinic (NE): 735-4901 (receptionist=Ellen, nurse=Iffat)
   - docs=Gayleen Jorgensen, Heather Baxter
6. Nancy Stocker: 944-4442
7. Alix Crossley: 541-7568
8. Ethics Board: 220-3782 (Pat Evans, ideally refer participant to David or Suzanne for this referral)
9. *67: to block call display when calling from home
10. *70: to shut off call waiting when calling from home
11. If patient requests emotional assistance: notify David, Suzanne, or Nancy immediately.

The number for the Crisis Line is 266-1605 (both mobile unit and call in); Calgary Counseling Centre=265-4980. Perinatal Bereavement Counselling Centre (for miscarriages, stillbirths etc…)=670-2248. Caring Beyond (support group for those who have experienced a stillbirth, miscarriage, or fetal demise)=294-1131

12. For questions related to meconium screening: Matt Hicks at 943-7539, 284-5951

**********If a participant asks any study related questions you cannot answer, please take their name and number and Matt Hicks (284-5951 or 943-7539) will call them back. All medical questions should be referred to participant(or potential participant's) doctor**********

Additional Interviewer Training Notes

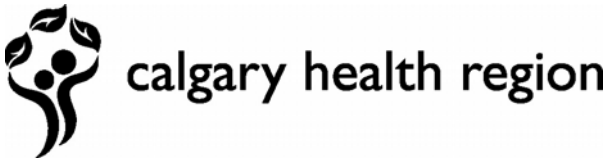
General comments:

- Confidentiality is critical. Unless you are directly talking to the person himself/herself, please do not mention any confidential details or the reason you are calling. **ONLY TALK DIRECTLY TO THE PATIENT HERSELF.**
- The interviewer's role is for data collection, not to provide emotional support, referrals, or clinical information. If woman have any questions about their pregnancy or clinical questions such as "where is the clinic", "can I change my first appointment", please ask the patient to call the clinic directly. However, if you do get the sense the woman may require emotional support/seems upset/or could harm herself or others, state "we realize that some of the questions in this questionnaire are sensitive…if you would like to talk to a distress or counseling centre, I have numbers you can call (then offer numbers).
- Importantly, if you do not know the answer to a question please take the patient's name and number and notify Matt Hicks immediately. He will call them back ASAP. Also, any clinical questions should be referred to their doctors, and mention "I am not a medical doctor, you will have to contact your medical doctors or nurses to ask that question"
- Tone of voice is critical: a very "neutral" tone of voice is important. Be aware that the tone of voice you have can influence opinion and answers. For example, by saying "ok" a lot after a patient answers, be aware and ask "am I saying this because I personally approve of this answer". After a patient answers a question, it is better to say "thank you" or simply go to the next question, rather than saying words like "yes", "mmm, hmmm", "hmmm", or "ok". It is

important that the participant does not feel she is being judged or does not feel there are "right" answers to questions. Of course an interviewer should not come across as "cold", the key is a neutral yet interested sounding voice and concentrate on listening. Words that may be tough for a participant to catch, like "NOT", should be clearly stated when reading questions.

- Sometimes a participant will say "what would you do?", or may return a sensitive question back to the interviewer (e.g. "have you been pregnant before?", "did this happen to you when you were pregnant?" etc… The best way to answer this is pleasantly say that you are not allowed to talk about yourself during an interview.
- It is not appropriate to talk about your own personal "life experiences" when interviewing. For example, it is not appropriate to talk about times you have been pregnant, what your children weighed at birth, how you felt during pregnancy etc… A skilled interviewer should build enough rapport and trust with the patient so the patient will be willing to share information, but should not try to be their "best friend". People feel most comfortable when knowing their answers are private and confidential, and if a woman feels to close to an interviewer, or feels she should give socially desirable answers, this can impact her answers. Never say to a participant something to the effect of "that happened to me too" etc…
- Pay close attention to answers that are given. If an answer seems odd (for example the woman states that 7 days pass between menstrual cycles, paraphrase the answer, i.e. read their answer back to them…but of course with a neutral tone of voice.)

A.1.7. Subject Enrolment Letter for the Meconium Screening Study



Dr. Suzanne Tough, Assistant Professor
University of Calgary & CHR
Pediatrics/Community Health Sciences
Alberta Children's Hospital
1820 Richmond Rd SW
Calgary, Alberta T2T 5C7

September 6, 2007

Subjects Name
Subject's Address
Calgary, Alberta
Postal Code

Dear Subject's Name

Thank you for taking part in the Meconium Screening part of the Community Perinatal Care Study. Your participation will help us answer important questions about maternal and child health. Attached to this letter you will see two pink study cards. Please **give a card to the nurse** when you are admitted to the hospital to deliver your baby. This will help identify you as a study participant. Place one card on your fridge as a reminder and for easy reference if you want to call us. We have also given you a copy of the consent form that was read to you over the phone a few days ago.

Please find enclosed the sample collection kit. Please place the kit in your hospital bag now. We would like you to take the kit to the hospital with you when you are in labor. If you forget the kit there will be spares at the hospital that the nurses can use. So, if you forget, please tell the nurse you are in the study and have forgotten your kit. The kit includes instructions for sample collection, sample collection materials, forms for hospital use, and a few diapers to get started. Please bring the complete kit to the hospital with you.

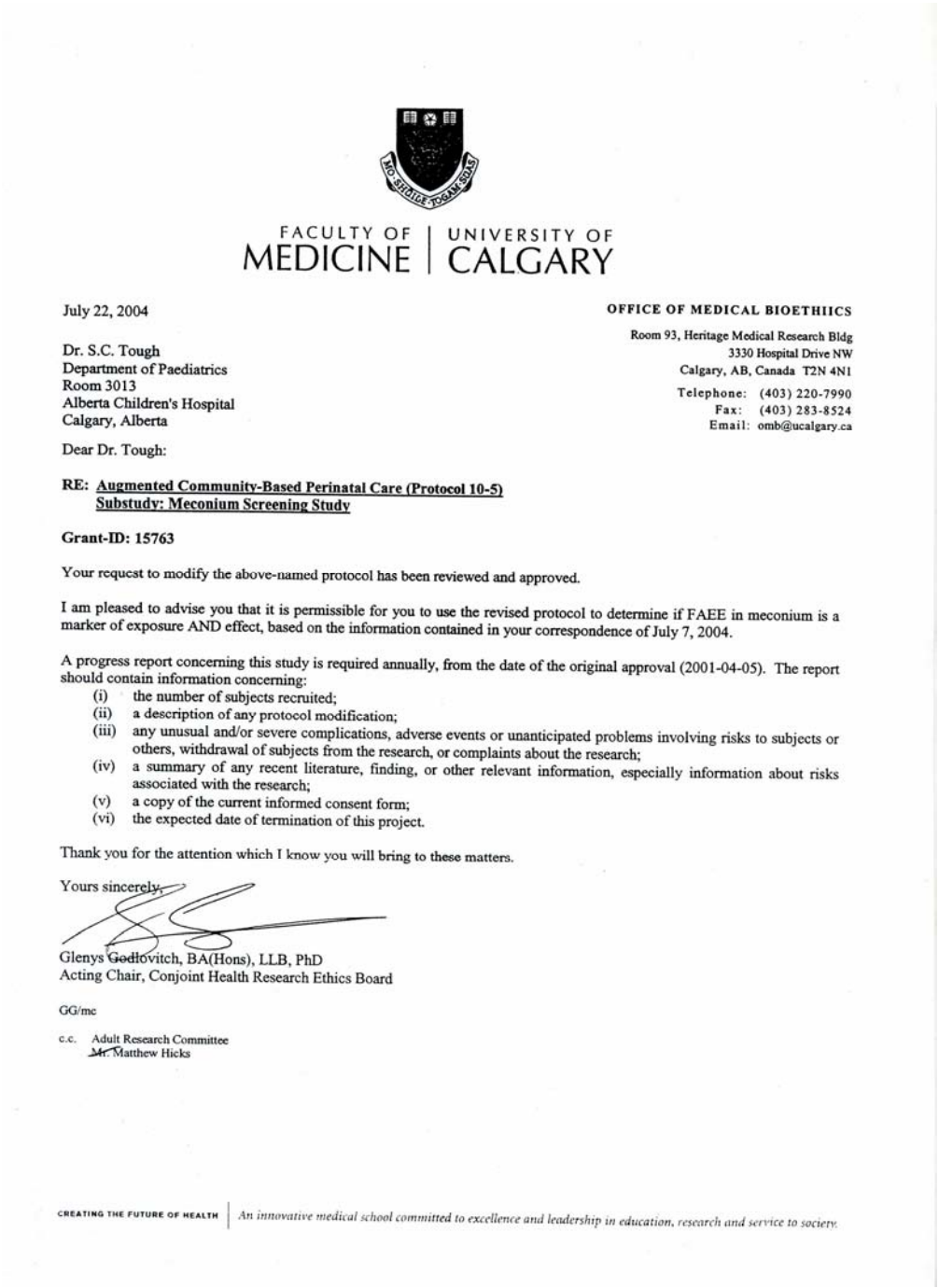
As we mentioned when we enrolled you, we will call you in the next few days to make sure that you have received the sample collection kit. We can also answer any additional questions at that time. In the meantime, if you have any questions please call the study coordinator, Matt Hicks, at 943-7539.

Best wishes on your up-coming delivery,

Matt Hicks
For Dr. Suzanne Tough

A.2. Biomarker in Meconium and Child Development

A.2.1. Ethics Approval for the Association between Child Development and Level of Biomarker as a Modification of the Community Perinatal Care Study



FACULTY OF MEDICINE | UNIVERSITY OF CALGARY

July 22, 2004

OFFICE OF MEDICAL BIOETHIICS
Room 93, Heritage Medical Research Bldg
3330 Hospital Drive NW
Calgary, AB, Canada T2N 4N1
Telephone: (403) 220-7990
Fax: (403) 283-8524
Email: omb@ucalgary.ca

Dr. S.C. Tough
Department of Paediatrics
Room 3013
Alberta Children's Hospital
Calgary, Alberta

Dear Dr. Tough:

RE: Augmented Community-Based Perinatal Care (Protocol 10-5)
Substudy: Meconium Screening Study

Grant-ID: 15763

Your request to modify the above-named protocol has been reviewed and approved.

I am pleased to advise you that it is permissible for you to use the revised protocol to determine if FAEE in meconium is a marker of exposure AND effect, based on the information contained in your correspondence of July 7, 2004.

A progress report concerning this study is required annually, from the date of the original approval (2001-04-05). The report should contain information concerning:

(i) the number of subjects recruited;
(ii) a description of any protocol modification;
(iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
(iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
(v) a copy of the current informed consent form;
(vi) the expected date of termination of this project.

Thank you for the attention which I know you will bring to these matters.

Yours sincerely,

Glenys Godlovitch, BA(Hons), LLB, PhD
Acting Chair, Conjoint Health Research Ethics Board

GG/mc

c.c. Adult Research Committee
Mr. Matthew Hicks

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A.2.2. Recruitment Forms: Association between Child Development and Level of Biomarker

CODES: To fill in before Call/
To Read Aloud (Min)
To fill in during the recruitment call
Additional Notes not in original form

1st Appt Date:
Home Number: Time:
Work Number: (only if already in SPSS) Confirmed □

Alt Contact Name: (only if already in SPSS) 2nd Appt Date:
Alt Contact Number: (only if already in SPSS) Time:
Confirmed □
Estimated DOB:

INTERVIEWER INSTRUCTIONS
Entire Instructions Must be Read to all Participants

Hello, may I please speak with _____?

Hello, Mrs./Ms ._____, my name is (Natarie Lui)_, and I am calling with the MEC Meconium STUDY which you participated in _____ (when) based with the Calgary Health Region and University of Calgary. Do you recall your earlier participation in our study?

In the MEC Study we collected a sample of your baby's meconium. Do you have any questions or comments about your experiences during that study?
_____
_____
_____

At the time of your enrolment in the MEC study, we told you that some participants may have the opportunity to participate in a follow-up assessment of their child with a paediatrician who specializes in child development. You indicated that you would be interested in being contacted for research related to developmental follow-up of your child. We are following up children that had positive samples and negative samples and looking at mental, motor, and behavioural development of children at 2 years of age. The majority of children that we are following up had negative samples. I am calling to tell you about the follow up component of the study and invite you to participate. Do you have a moment so I that could explain more about this project? (*If no, ask when a more convenient time would be.)*

(if participant asks if their infants sample is positive or negative, let them know that you do not have access to the information but that the results will be made available to them when the study is completed)
Date of follow up call: ____ month ____ day _____ year

Time of Day: Morning Afternoon Evening

Check a box every time try to reach patient under appropriate time (i.e. to assess participation):

8am-6pm □

7pm-9pm □

1. Approximately 20-40% of women in Canada use alcohol during pregnancy and 3-15% use drugs during pregnancy. Currently, there is a lack of research about objective tests or screens to reliably identify infants at risk for health and developmental problems related to maternal drug and/or alcohol use. The purpose of this project is to see if there is an association between the level of biomarker found in an infant's meconium and their cognitive, physical, and behavioural development at 24 months of age.

2. Your participation in the follow up component will aid us in the identification of infants who might benefit from extra help early in their childhood, the implementation of strategies or programs to modify maternal behaviour during future pregnancies and in providing policy makers, clinicians, and researchers with important information to improve maternal and child health in the Calgary Health Region.

3. We have 2 levels of participation – Our Binder Only level of participation involves a Study Binder being sent to you to fill out. This contains 10 questionnaires investigating various aspects of your child's development, most participants report that they have found it to take them a total of about 3 hours to complete.
   We also hope that you may consider enrolling at our Full Participation level. This involves completing not only the Study Binder, but also 4 Follow Up assessments
   The follow-up component of this study will involve 2 visits to the Alberta Children's Hospital at 24 months of age where your child will be assessed by a paediatrician, a clinical psychologist and a speech language pathologist. In addition, a digital photo will be taken of your child for facial analysis. Because a child's thought processes and problem solving skills are often very similar to their mother's, we will also be doing a brief assessment with you. This assessment involves four components, vocabulary, similarities, block design, and matrix reasoning. Prior to the visit, we will be asking you to fill out some forms with questions about your pregnancy and about your child. We expect that these visits will take several hours from your day but we will reimburse you for transportation, child care, and meals on site. Therefore, it is anticipated that you will incur no financial costs by participating in this study.

4. Participation in the study does not preclude standard of care for the children. Developmental paediatricians will refer subjects for treatment or further testing as indicated.

5. You told us in an earlier questionnaire what your diet and lifestyle were like during pregnancy and we would then link the results of the psychological tests to what you told us in the telephone questionnaires. We will also collect information related to these factors again. In the earlier study we linked questionnaire results with obstetrical and birth records as well as meconium lab results and will continue to do so for this part of the study.

6. We would also like to access your child's pediatric and primary care physician records. This information will be used for study linkage and will only be made

available to study team members.

7. This project does not involve any medical procedures. All information will be kept private and confidential, and will not be made available to your regular doctors unless you consent. Only study team members will have access to the results of the meconium analysis.

8. There are no short or long-term risks associated with the visit with the paediatrician or with the psychological testing. This testing is play-based and should be enjoyable for your child.

(*if the participant asks about who has access to the meconium analysis results, read the following:*

The sample will be identified by the study identification number that was assigned to you when you were enrolled in the study. The meconium analysis results will be linked to the information you provided in the telephone questionnaires. This information will not become part of your or your infant's medical record. Only the study team members will have access to the results of meconium analysis. Prior to analysis, any variables that identify you will be removed from the data set. Only the principal investigators or their delegates will be able to link results of laboratory findings to the study data base.)

9. At any time you can discontinue participation.

<Ask if they have any questions and confirm that they understand what their involvement would be. Then ask if they are interested in participating.>

This consent process is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, you should feel free to ask.

Do you consent to participate in the Meconium Follow-up Study? This will involve 2 visits to Alberta Children's Hospital for testing and questionnaires that you will be asked to complete in advance of the visits to Alberta Children's Hospital.
(If participant indicates that she wants more information before deciding, tell her that an information package will be sent to her.
If participant wants to talk it over with partner to decide, ask when a good time to call back would be)

Participate: Yes No

Date of Enrolment for follow up study: _____month _____day _____year

Since we are on the phone, so that I may indicate that you have given verbal consent to participate in the Meconium 24 Month Follow Up Study , I need to document your mother's maiden name.
For the women who consent, we ask that they identify their mother's maiden name for our records. This will be used to identify that you did provide verbal consent.
Maiden name of the mother of the subject: _____

Could you provide us with your Alberta Health Care Number? (Can get later when booking appt if time is running out) _____

In preparation for the follow up visit we would like to ask you several questions about

your child:
Name: _____

Sex: [1] male
[2] female
[8] don't know [9] no answer

Date of birth : _____month _____day _____year

Birth weight: _____grams or __pounds___ounces (Can get later but try to get now)
_____don't know
_____no answer

How many weeks pregnant were you at the time of delivery? (40 is Full Term, round to _____weeks the nearest half week – Can get later but try to get now)
_____no answer
_____don't know

Could you provide us with your child's personal health number for access to the Alberta Children's Hospital?
_____ (9 digits) Child's PHN

In the event that the pediatricians feel that follow up is required on anything found we would like your permission to contact your family physician with a brief report and referral recommendations.

Do you consent for the release of this information as warranted: Yes No

Could you provide us with the name of your child's primary health care physician?
Name: _____ Child's Family Doc

We are planning to conduct the follow-up appointments at the Alberta Children's Hospital. Our Developmental Paediatricians and Psychologists hold clinic there. Clinic days are scheduled for Friday and Saturday mornings generally. The Pediatrician appointment is offered on select days during the week only. **and the occasional Monday and Saturday. The follow up** assessments **component** total **approximately four hours, which we divide into two visits.**

We would like to follow your child up sometime between 21 and 27 months of age.
Which days and times would be most convenient for you?
Would a Friday be possible for you?
If not, would you prefer a Monday or Saturday?
Time of Day: Morning Afternoon Early Evening

Preferred **Day : _____** Preferred **Time: _____**

As I mentioned earlier, we will provide babysitting services at no cost to you. Would you require this service?
Babysitting: Yes No
Would you prefer babysitting at Alberta Children's Hospital during your appointment or to be compensated for babysitting at your home?
Babysitting – Location Preferred **On site Home**

(Reminder: Childcare by Coordinator, MRC Child Studies Student, or Emily's Backyard)

If on site babysitting will be provided:
Name of child: _____ Age of child: _____
Name of child:_____ Age of child:_____

We will also be reimbursing you for transportation costs and/or parking expenses. Will you require a taxi or do you have your own vehicle?

_____Taxi (If Taxi, Please use Black Top Cabs, 291-3456)
_____Own Vehicle (If own vehicle, for parking please use underground parkade and if full use meters out front.)

Do you or your child have any special diet requirements for the meal(s) that will be provided for you?
We provide a snack during childcare periods, does your son/daughter have any food allergies or special diet requirements?
_____[1]Vegetarian _____[2] Lactose -intolerant
_____[3] Nut allergy [4] Other: _____
Also a 'None' Option which was not entered in original form None: _____

Do you have any questions or comments?

I **We will be sending out** the Study Binder to you shortly**, questionnaires to your home, Can I please confirm your address?**
Street_____
___
City_____
__
Postal
Code_____

Enclosed within this package will be my contact information. Please do not hesitate to call me should you have any further questions or concerns. I will be phoning you in a few weeks time to set up the first appointment session.

The Binder with the study questionnaires will be_____ Delivered
_____Mailed to you.
Thank you, again, for your participation in this study. Feel free to contact us if you have any additional questions or concerns between now and your appointment. My name is _____ and can be reached at 955-7539.

In the event that you move or change your contact info, can we get the name and phone number of someone else who we could contact? This could be a cell phone number or a family member.

Alternate Contact (name)_____
(number)_____
Thank you very much for your time**. and have a great day.**

A.2.3. Consent Forms: Association between Child Development and Level of Biomarker

STUDY CONSENT FORM
ALBERTA CHILDREN'S HOSPITAL COPY

Study Title: Community Perinatal Care Study – **Meconium Screening Follow up Study**
Principal Investigator: S Tough
Co Investigators: M Hicks, R Sauve, A Lyon, M Clarke, B Gibbard, R Brant, D Creighton
Sponsor: Alberta Children's Services and the Alberta Heritage Foundation for Medical Research

At the time of your enrolment in the Meconium Screening study, we told you that some participants may have the opportunity to participate in a follow-up assessment of their infant with a paediatrician who specializes in child development. You indicated that you would be interested in being contacted for research related to developmental follow-up of your infant. We are following up all infants to look at mental, motor, and behavioural development at 2 years of age. The majority of children that we are following up had negative meconium samples. As read to you during a recent phone conversation, this consent form provides additional information about the follow-up project.

1. Approximately 20-40% of women in Canada use alcohol during pregnancy and 3-15% use drugs during pregnancy. Currently, there is a lack of research about objective tests or screens to reliably identify infants at risk for health and developmental problems related to maternal drug and/or alcohol use. The purpose of this project is to see if there is an association between the level of biomarker found in an infant's meconium and their cognitive, physical, and behavioural development at 2 years of age.

2. The follow-up component of this study will involve 1 or 2 visit(s) to Alberta Children's Hospital at approximately 2 years of age where your infant will be assessed by a paediatrician, a speech language pathologist and a psychologist. In addition, a digital photo will be taken of your infant for facial analysis. Because a child's thought processes and problem solving skills are often very similar to their mother's, we will also be doing a brief assessment with you. This assessment involves four components, vocabulary, similarities, block design, and matrix reasoning. Prior to the visit(s), we will be asking you to fill out some forms with questions about your pregnancy and about your infant. We expect that this visit(s) will take several hours but we will reimburse you for transportation, child care, and meals on site. Therefore, it is anticipated that you will incur no financial costs by participating in this study.

3. Your participation in the follow up component will aid us in the identification of infants who might benefit from extra help early in childhood, the implementation of strategies or programs to modify maternal behaviour during future pregnancies and in providing policy makers, clinicians, and researchers with important information to improve maternal and child health in the Calgary Health Region.

4. Participation in the study does not preclude standard of care for children. Developmental paediatricians will refer infants for treatment or further testing as indicated. In the event that the paediatricians feel that follow up is required we would like your permission to contact your family physician with a brief report and referral recommendations.

Do you consent for the release of this information as warranted: **Yes** **No**

5. You told us in an earlier questionnaire about your diet and lifestyle and we will link the results of these assessments to this information. We will also collect information related to these factors again. In the earlier study we linked questionnaire results with obstetrical and birth records as well to meconium lab results and will continue to do so for this part of the study. We would also like to access your child's paediatric and primary care physician records. This information will be used for verification and will only be made available to study team members.

6. This project does not involve any medical procedures. All information will be kept private and confidential, and will not be made available to your regular doctors and nurses. Only study team members will have access to the results of the analysis.

7. There are no short or long term risks associated with the visit with the paediatrician or with the psychological testing. This testing is play-based and should be enjoyable for your child.

8. Prior to analysis, any variables that identify you will be removed from the data set. Only the principal investigators or their delegates will be able to link results of laboratory findings to the study data base.

9. At any time you can discontinue participation.

10. In the event that you suffer injury as a result of participating in this research no compensation will be provided for you by the principal investigators, the University of Calgary, or the Calgary Health Region. You still have all your legal rights. Nothing said here about treatment or compensation in any way alters your right to recover damages."

This consent process is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, you should feel free to ask.

Your written consent indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time without jeopardizing your health care. Your continued participation should be as informed as your initial consent, so you should feel free to ask for clarification or new information throughout your participation.

_____	_____
Name of Participant (please print)	Signature of Participant
_____	_____
Name of Witness (please print)	Signature of Witness
_____	_____
Signature of Investigator/Study Delegate	Date/Time

If you have further questions concerning matters related to this research, please contact:

Matt Hicks, Study Coordinator	Dr. Suzanne Tough	Dr. Andrew Lyon
	Project Investigator	Project Investigator
University of Calgary	University of Calgary	University of Calgary
Phone: (403) 955-7539	Phone: (403) 955-2772	Phone: (403) 209-5205

If you have any questions concerning your rights as a possible participant in this research, please contact Pat Evans, Associate Director, Internal Awards, Research Services, University of Calgary, at 220-3782.

A.3. Maternal Willingness to Consent

A.3.1. Scientific Approval of Maternal Willingness to Consent Study

Foothills Medical Centre
1403 29 Street NW
Calgary, Alberta, Canada T2N 2T9
website www.calgaryhealthregion.ca

calgary health region
Foothills Medical Centre

30 June 2003

Dr. Suzanne Tough
Department of Community Health Sciences
University of Calgary

Dear Dr. Tough:

Re: #16979 - The Conditions Under Which Women in the Calgary Health Region Will Consent to Alcohol and Drug Screening of Their Infants

Thank you for submitting an application regarding the above project for review by the Adult Research Committee of the Calgary Health Region (CHR). This will confirm that the committee has granted institutional approval for this project, and that the CHR has granted approval under Sections 53 and 54 of the Health Information Act. **This approval is contingent on approval by the Conjoint Health Research Ethics Board.**

It is understood from your submission that your study will be entirely funded through external sources and that the CHR will be reimbursed for all research costs associated with this project. To facilitate a smooth startup of your project, please notify affected departments in the Region well in advance of your intent to initiate this study.

Please note that it is a requirement that you communicate in writing the study results to the CHR Adult Research Committee, and provide any copies of publications arising from the research as well as provide feedback regarding any problems encountered during the course of the study.

Please accept the committee's best wishes for success in your research.

Yours sincerely,

John Jarrell, MD
Chair, Adult Research Committee

cc: Dr. R. Sauve, Conjoint Health Research Ethics Board

A.3.2. Ethics Approval for Maternal Willingness to Consent Study

Office of Medical Bioethics
Heritage Medical Research Building/Rm 93
Telephone: (403) 220-7990
Fax: (403) 283-8524

March 31, 2003

Dr. S.C. Tough
Department of Paediatrics
Room 3013
Alberta Children's Hospital
Calgary, Alberta

Dear Dr. Tough:

RE: The Conditions Under Which Women in the Calgary Health Region Will Consent to Alcohol and Drug Screening of Their Infants Student: Matthew Hicks Degree: PhD

Grant-ID: 16979

The above-noted thesis proposal, including Appendex B2: Draft enrolment script for focus groups for Part B, Appendex B3: Draft information sheet for focus group for Part B, Appendex B4: Draft consent form for focus group for Part B, Appendex B5: Draft consent form for survey for Part B, and recruitment posters (2), has been submitted for Committee review and found to be ethically acceptable. Please note that this approval is subject to the following conditions:

(1) a copy of the informed consent form must have been given to each research subject, if required for this study;
(2) a Progress Report must be submitted by 2004-03-31, containing the following information:
  (i) the number of subjects recruited;
  (ii) a description of any protocol modification;
  (iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
  (iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
  (v) a copy of the current informed consent form;
  (vi) the expected date of termination of this project;
(3) a Final Report must be submitted at the termination of the project.

Please note that you have been named as a principal collaborator on this study because students are not permitted to serve as principal investigators. Please accept the Board's best wishes for success in your research.

Yours sincerely,

Christopher J. Doig, MD, MSc, FRCPC
Chair, Conjoint Health Research Ethics Board

cc: Child Health Research Committee Dr. B. Scott (information) Mr. Matthew Hicks

A.3.3. Recruitment Poster for Maternal Willingness to Consent Focus Groups

Come out and share your views, thoughts, attitudes and feelings, in a group interview, about alcohol and drug testing of babies.

Refreshments and snacks will be served.

Please call Matt Hicks,

943-7539 if you are interested or have any questions.

A.3.4. Recruitment Script for Maternal Willingness to Consent Focus Groups

The conditions under which women will consent to alcohol and drug screening of their infants

Recruitment Screening Tool

Hello. My name is Jennifer, I'm a researcher from the University of Calgary. A group of researchers in the Calgary Health Region are looking for women who are interested in talking about their thoughts and views on alcohol and drug testing of babies. We think it is really important that the opinions of women are heard.
Talking about these things will help doctors and nurses understand women's feelings about this sort of testing. I have an information sheet that tells you more about the study. Can I ask you some questions to see if there is a match between your experience and the needs of our study? [If the woman gives verbal consent, please continue. If not, thank her for her time. Please be discrete and try not to conduct the screening in the middle of the waiting room.]

Confidentiality will be maintained. Women will be offered food and refreshments and reimbursement for parking, transportation, and babysitting costs. Would you like to sit down in a group with several other women and talk about this issue? Yes_____ No _____.

Is it convenient for you to come to CUPS? Yes_____ No_____

We will arrange to have babysitters on site.
Would you use the babysitter that we provide? Yes_____ No_____
If 'YES', How many children should we expect?_____

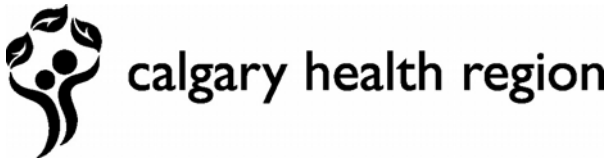
The focus group will be held here at CUPS on Wednesday May 28th from 1 to 3 pm.

Recruiter: Obtain woman's name and phone number(s). Give her an information sheet. We would like to call you to remind you about the focus group.

Name: _____

Home Phone Number: _____
Cell Number: _____
Recruiter observational screening:
Does the woman speak English? Yes_____ No _____.
Does she seem interested in sharing her thoughts? Yes_____ No _____.
Does she volunteer information about her experience? Yes_____ No _____.

A.3.5. Information Sheet for Maternal Willingness to Consent Focus Groups



Title of the Project: The conditions under which women will consent to alcohol and drug screening of their infants

Investigators: AW Lyon, S Premji, SC Tough

Funding: The study is funded by Alberta Children's Services

Purpose: This study will allow us to learn more about when women would agree to have their infant screened for exposure to alcohol and drugs.

Background: Methods that will allow testing of mothers and infants for alcohol and drug exposure exist. However, there is limited research on the acceptability of this testing among women. We are interested in determining under what conditions women may consent to testing.

Procedures: If you agree to take part in this focus group you will be interviewed once in a group with other women who are pregnant or who have recently delivered a baby. The interview will be tape recorded. The group leader will ask you questions about what you think about alcohol and drug testing in infants. The information will be used to develop a questionnaire for use among a larger group of women in the Calgary.

Benefits and Risks: There are no known risks or direct benefits to you if you participate in the study. The results from the study will help health care providers understand what factors contribute to a woman's decision to accept or reject alcohol and drug testing of their infant. The results will also help us identify women's attitudes to such testing.

Ethics: This study has received ethical approval.

Confidentiality: Everything you say in the interview will remain confidential. Only the researchers will have access to the information. The information you give will be combined with information from other participants. Any results that are published or presented will not identify you.

Freedom to Withdraw: Participation is voluntary and if you decide not to participate, your health care will not be affected. You have the right to withdraw from the study at any time, as well as the right to refuse to answer any of the questions.

Additional Contacts: If you have further questions you can contact Matt Hicks at (403) 943-7539 or Dr. Suzanne Tough at (403) 943-2272. If you have concerns about how this

study is being done, you can contact Pat Evans, Associate Director, Internal Awards, Research services, University of Calgary at (403) 220-3782.

Focus Group

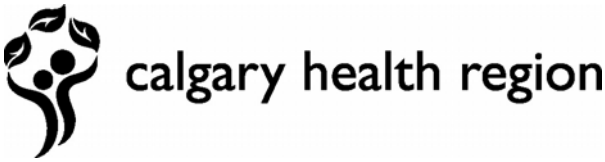
WHEN: Wednesday May 28th
TIME: 1 to 3 pm
WHERE: CUPS

We will provide you with food and refreshments and pay you for any costs related to transit, parking or babysitting. We will have a babysitter on the 2nd floor of CUPS who can look after your children if you notify us in advance.

Questions or Comments?
Call Matt at 943-7539 or speak to Lysanne in the Family Resource Centre at CUPS Tuesday to Thursday.

Thank you.

A.3.6. Consent for Maternal Willingness to Consent Focus Groups



CONSENT FORM

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Co-Principal Investigators: AW Lyon, S Premji, SC Tough
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This consent form, a copy of which has been given to you, is only part of the process of informed consent. It should give you the basic idea of what the research project is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, please feel free to ask. Please take the time to read this form carefully and to understand the following information.

You are being asked to participate in this focus group as part of the process of developing a survey questionnaire which will ultimately be answered by over 1500 women. The purpose of the focus group is to allow us to better understand perceptions, attitudes, opinions and beliefs on alcohol and drug screening of infants.

If you agree to participate in this study, you will be interviewed in a group and the responses you provide will be audio taped. These responses will be transcribed verbatim (word for word) and the information may be used to develop the survey questionnaire.

There are no known risks associated with this study and you are free to withdraw at any time.

Anything you may say in the taped interview will remain confidential. Only the researchers will have access to the original study information. The information collected will be combined with information from other participants. Any results that are published or presented will not identify you or your infant in the findings.

Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the focus group and that you agree to participate as a subject. In no way does this waive your legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time. If you have any further questions concerning matters related to this research, please contact: Matt Hicks at 943-7539 or Dr. Suzanne Tough at 943-2272.
If you have any questions concerning your rights as a possible participant in this research, please contact Pat Evans, Associate Director, Internal Awards, Research Services, University of Calgary at 220-3782.

Should you find the focus group to be an emotionally difficult experience you can obtain support through contacting the Crisis Line at (403) 266-1605, or the Calgary Counselling Centre at (403) 265-4980, the Perinatal Bereavement Counselling Centre at (403) 670-2248 or Caring Beyond (403) 294-1131.

Are you willing to be contacted for additional research?

Yes____ No_____

If yes, home phone number: _____
cell phone number:_____

_____
Participant's Name

_____
Participant's Signature **Date**

_____
Investigator's and/or Delegate's Name

_____
Investigator's and/or Delegate's Signature **Date**

_____
Witnesses Name

_____
Witnesses Signature **Date**

Demographic Information

We would like to collect some basic information in order for us to be able to describe the participants of the focus groups without using names or other identifying information.

1. Participant's Age_____

2. Number of Children_____

3. Highest grade of school completed_____

Thank you.

A.3.7. Information Card for Maternal Willingness to Consent Cross-Sectional Survey

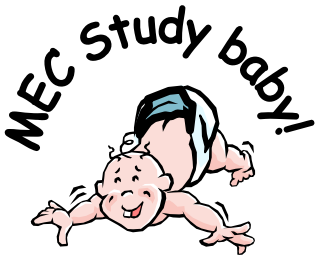
CONGRATULATIONS on the birth of your baby!

We would like to talk to you!

The Calgary Health Region and the University of Calgary are conducting research on women's opinions and attitudes about drug and alcohol screening of their infants. Tests have been developed to screen newborns for drug and alcohol use. No one has asked women what they think or feel and we believe this is very important. The results of this study will inform policy-makers and care providers about the issues involved in alcohol and drug screening.

Your nurse will be coming to ask you if a researcher can come and speak to you briefly about this issue.

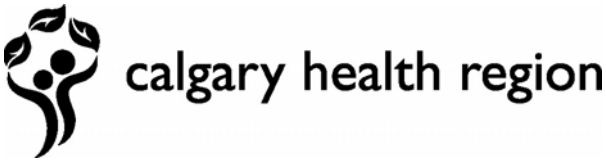
Thank you!



If you have any further questions concerning matters related to this research, please contact: Matt Hicks at 943-7539 or Dr. Suzanne Tough at 943-2272

Should you find the survey to be an emotionally difficult experience you can obtain support through contacting the Crisis Line at 266-1605, or the Calgary Counseling Center at 265-4980, the Perinatal Bereavement Counseling Center at 670-2248 or Caring Beyond at 294-1131.

A.3.8. Consent Form for Maternal Willingness to Consent Cross-Sectional Survey



CONSENT FORM

Title: The conditions under which women will consent to alcohol and drug screening of their infants
Co-Principal Investigators: AW Lyon, S Premji, SC Tough
Funding: This study is funded by Alberta Children's Services.

This consent form, a copy of which has been given to you, is only part of the process of informed consent. It should give you the basic idea of what the research project is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, please feel free to ask. Please take the time to read this form carefully and to understand the following information.

You are being asked to participate in this survey that is being given to all women currently on postpartum units in the Calgary Health Region. The purpose of the survey is to allow us to better understand women's attitudes and perceptions to drug testing as well as the conditions under which a woman would consent to alcohol and drug screening of infants.

If you agree to participate in this study, the research assistant will read a short list of questions and record your responses. The questions asked relate to conditions under which a woman would give consent for her infant to be tested for alcohol and drug exposure. Several short scenarios will be presented to you and you will be asked to choose a response. The research assistant will also ask for some demographic information and some questions related to your pregnancy and to drinking and drug use during pregnancy.

There are no known risks associated with this study and you are free to withdraw at any time.

Everything learned from you in the survey will remain confidential. Only the researchers will have access to the original study information. The information collected will be combined with information from other participants. Any results that are published or presented will not identify you or your infant in the findings.

Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the survey and that you agree to participate as a subject. In no way does this waive your legal rights nor release the investigators, sponsors, or

involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time. If you have any further questions concerning matters related to this research, please contact: Matt Hicks at 943-7539 or Dr. Suzanne Tough at 943 2272.

If you have any questions concerning your rights as a possible participant in this research, please contact Pat Evans, Associate Director, Internal Awards, Research Services, University of Calgary at 220-3782.

Should you find the survey to be an emotionally difficult experience you can obtain support through contacting the Crisis Line at (403) 266-1605, or the Calgary Counselling Centre at (403) 265-4980, the Perinatal Bereavement Counselling Centre at (403) 670-2248 or Caring Beyond (403) 294-1131.

Participants Signature **Date**

Investigator and/or Delegates Signature **Date**

APPENDIX B: DATA COLLECTION INSTRUMENTS

B.1. Association between Maternal Self-Report of Drug and Alcohol Use and Biomarker in Meconium

B.1.1. Community Perinatal Care Study Questionnaire #1

Study ID: _____

ning Study

DSRT

UNIVERSITY OF CALGARY

Questionnaire #1
(Completed at study intake)

TABLE OF CONTENTS

INTERVIEWER INSTRUCTIONS
Entire Instructions Must be Read to all Participants

Hello, may I please speak with _____?

Hello, Mrs./Ms ._____, my name is _____, and I am calling with the Calgary Health Region and University of Calgary.

You may recall talking to me a short while ago about a new study we are conducting on Meconium Screening. When we last talked, you mentioned you would be willing to be in this study and do an interview over the telephone today, is this still a good time to talk? (continue if yes) (If no, when would be a good time to call you back?)

Time for callback:
. Date of follow up call: ____month ____day _____year

Check a box every time try to reach patient under appropriate time (i.e. to assess participation):
8am-6pm □
7pm-9pm □

Just as a reminder, the study involves completing 2 questionnaires by telephone, one late the pregnancy and one about 2 months after babies in the study are born. Your responses will help us in our efforts to design and offer programs for improving pregnancy outcomes and enhancing infant and family health.

Read for phase 1 recruitment only: [the information you provide in the questionnaires will not be made available to anyone, including your regular medical doctor and nurses].

All women in this study continue to see their regular doctors and nurses. No woman who participates in this study, or her baby, will receive any less medical or community care than they would have received if they had not participated in the study. You should discuss any medical concerns or questions you have with your regular doctors and nurses. Do you have any questions?

Before we begin, I would just like to remind you that all of the information you provide is private and confidential and will only be available to the study team. You can withdraw from the study at any time. Your decision to complete this questionnaire will be interpreted as your continued consent to participate. You do not have to answer any questions that you do not want to answer. Please feel free to ask questions. We ask all women in this study these questions, and there are no right or wrong answers. Some of the questions may also be asked at your doctor's visit. If you need to take a break, please let me know.
If anything we discuss is upsetting, you can obtain emotional support by contacting the crisis line, the Calgary counseling centre, the perinatal bereavement centre, or caring beyond. I can provide you with the phone numbers for these agencies if you would like them.

If participant requests further information provide the following...
If you have further questions concerning matters related to this research, please contact:

Matt Hicks	Dr. Suzanne Tough	Dr. Andrew Lyon
Study Coordinator	Project Investigator	Project Investigator
University of Calgary	University of Calgary	University of Calgary
Phone: (403) 943-7539	Phone: (403) 943-2772	Phone: (403) 209-5205

-- This study is funded by Alberta Children's Services

Study ID: _____ Date Interview Completed: month ____ day____ year_____

Start Time of Interview: _____ Interviewer: _____

Interviewer note: do not offer don't know or no answer options to participant. Encourage participant to give best guess if she indicates don't know. Clearly circle or complete all answers. For scales, participants cannot pick middle/partial/decimal numbers, e.g. cannot pick 4.5 on a scale of 1-5.

PART ONE. MEDICAL

LMP: source: CPNP

1. What was the first day of your last menstrual period? ____day ____month _____year
___don't know *(best guess ok)*
___no answer

2. Do you know when your due date is? __ yes: ___day ___month ___year
__ no
___no answer

3. On average, how long is it from day 1 of your menstrual period to day 1 of the next menstrual period?
_____days ___don't know *(best guess is ok)* ___ no answer

Height: source: CPNP

4. How tall are you (without shoes, your best guess is ok)?
____(Feet) ____(Inches) or ____(Centimetres) or ____Don't know or ____No answer

Weight:

5. How much did you weigh at the beginning of this pregnancy (your best guess is ok)?
_____ Pounds or _____ Kilograms or _____ Don't know or _____No answer

6. How much do you weigh at this point in your pregnancy (your best guess is ok)?
_____ Pounds or _____ Kilograms or _____ Don't know or _____No answer

Prenatal Care: source: new question

7. How many weeks pregnant were you when you:

7a. Were sure you were pregnant by home pregnancy test or doctor visit? ___weeks pregnant
___don't know
___no answer

7b. Contacted your doctor to book the appointment for your first prenatal physical examination?
___weeks pregnant ___don't know ___no answer

7c. Had your first prenatal physical examination with your doctor?
___weeks pregnant
___ I have not had my first prenatal physical examination with my doctor yet
___ don't know
___no answer

PART TWO. PREVIOUS PREGNANCIES

I would now like to ask you about other times you may have been pregnant BEFORE YOUR CURRENT PREGNANCY. In other words, these questions are about previous times you may have been pregnant, not your current pregnancy.

1. Have you ever been pregnant before? (including previous adoptions, miscarriages, stillbirths, or abortions)
[1]Yes ⇒ how many times have you been pregnant before this pregnancy?: _____
[2]No *(if "no", go to Part Three of the questionnaire, page 10)*
[8] Don't know *(if "don't know", go to Part Three, page 10)*
[9] No answer *(if " no answer", go to Part Three, page 10)*

interviewer: number pregnancies consecutively and use for questions below (e.g. preg#1, #2, #3)

2. Have you ever had a pregnancy end in... *(interviewer: ask phrase "have you ever had..." for 2a-2c)*

2a. A miscarriage? [1]Yes [2]No [8]Don't know [9] No answer Preg# Weeks
└how many previous miscarriages have you had? _____ _____ _____ _____

2b. An abortion? [1]Yes [2] No [8]Don't know [9] No answer
└how many previous abortions have you had? _____ Preg#(s):_____

2c. A still birth? [1]Yes [2]No [8]Don't know [9] No answer
⌊how many previous still births have you had? _____ Preg#(s):_____

3. In any of your PREVIOUS PREGNANCIES did you: *(interviewer: ask phrase "in any...before 3a-3b)*

_____

3a. Attend prenatal classes? [1]Yes [2] No [8] Don't know [9] No answer |*interviewer: if participant*
|*mentions she attended a* |*perinatal class (covers both* _____|*check "yes" to both*
3b. Attend parenting classes? [1]Yes [2] No [8] Don't know [9] No answer |*prenatal & antenatal period)*

In any of your PREVIOUS PREGNANCIES did you: *(interviewer: ask phrase "in any...before 3c-3f)*

3c. Drink alcohol?
[1] Yes [2] No *(if no, go to 3d)* [8] Don't know *(go to 3d)* [9] No answer *(go to 3d)*
⌊ i. In which pregnancies did you drink alcohol? _____*(enter preg#s)*
ii. How often, on average, did you drink an alcoholic beverage? If you drank alcohol in more than one previous pregnancy, think about the most recent pregnancy you drank.

[1] Every day----------
[2] 4-6 times per week | *If participant mentions only drank before*
[3] 2-3 times per week | *knew was pregnant, still ask questions*
[4] Once a week | *on frequency but check this box:* ☐
[5] 2 to 3 times a month | *(not directly asked)*
[6] Once a month | *Comments:*
[7] Less than once a month----------
[8] Don't know
[9] No answer
⇓

iii. On the days you drank alcohol in a previous pregnancy, how many drinks per day did you usually have? By a "drink", we mean one bottle/glass/can of beer, one glass of wine or one wine cooler, or one drink/highball/cocktail with 1 ounce of liquor)
_____*(enter average # drinks per day)*

(interviewer: ask question referring to most recent pregnancy drank alcohol. If a range is given, e.g. 2-4, enter the average amount, e.g. 3, and write range belowthe space that is provided. It is ok to enter "a few sips" or "1/2 drink if offered)

3d. Smoke at least one whole cigarette?
[1] Yes [2] No *(go to question 3e)* [8] Don't know *(go to 3e)* [9] No answer *(go to 3e)*
⌊ i. In which pregnancies did you smoke? _____*(enter preg#s)*
⌊ ii. How often, on average, did you smoke cigarettes? If you smoked cigarettes in more than one previous pregnancy, think about the most recent pregnancy that you smoked.

[1] Every day----------
[2] 4-6 days per week | *check if only smoked before knew pregnant:* ☐
[3] 2-3 days per week | *(not directly asked)*
[4] Once a week | *Comments:*
_____
[5] Less than once a week___ |

iii. On the days you smoked, how many cigarettes did you usually smoke per day? _____*(enter average # cigarettes per day)(1 pack=25 cigs)*

(interviewer: ask question referring to most recent pregnancy smoked. If a range is given, e.g. 10-15, enter the average amount, e.g. 12.5, and write range below
the space that is provided. It is ok to enter "a few puffs" or "1/2 cig if offered)

3e. Use street drugs such as marijuana or cocaine?
[1] Yes [2]No *(if no, go to question 4.)* [8] Don't know *(go to 4)* [9] No answer *(go to 4)*
⌊i. In which pregnancies did you use street drugs? _____(enter preg#s)
ii. Which street drugs did you use? If you used street drugs in more than one previous pregnancy, think about the most recent pregnancy you used street drugs *(check all that apply)*

__ Marijuana or Hashish (hash, pot, hash oil, hash putty)
__ Cocaine or crack (coke, rock)
__ Heroin (smack, horse)
__ Tranquilizers (downers, ludes)
__ Stimulants: amphetamines (uppers, speed, crystal)
__ Psychedelics/Hallucinogens: mushrooms, LSD/Acid, PCP/Angel Dust, Ecstasy
__ Inhalants: glue, gas, toluene, hairspray, other aerosols
__ Other
*(Specify)*_____

⌊ iii. How often, on average, did you use street drugs? If you used street drugs in more than one previous pregnancy, think about the most recent pregnancy you used street drugs.

[1] Every day_____
[2] 4-6 days per week | *check if only used drugs before knew pregnant:* ☐
[3] 2-3 days per week | *(not directly asked)*
[4] Once a week | *Comments:*
_____
[5] 2 to 3 times a month |
_____
[6] Once a month |
_____
[7] Less than once a month | _____
[8] Don't know |
[9] No answer_____|

4. We will now complete a table about previous LIVE BIRTHS. *(interviewer: Please write on the margin of back of this page if more space is needed):*

	Baby#1	Baby#2	Baby#3	Baby#4
Sex(male or female)	[1] male [2] female [8] don't know [9] no answer	[1] male [2] female [8] don't know [9] no answer	[1] male [2] female [8] don't know [9] no answer	[1] male [2] female [8] don't know [9] no answer
Date of Birth	____day ____month ____year ____don't know ____no answer	____day ____month ____year ____don't know ____no answer	____day ____month ____year ____don't know ____no answer	____day ____month ____year ____don't know ____no answer
How much did this baby weigh at birth?	_____grams or __pounds___ounces ___don't know ___no answer	_____grams or __pounds___ounces ___don't know ___no answer	_____grams or __pounds___ounces ___don't know ___no answer	_____grams or __pounds___ounces ___don't know ___no answer
How many weeks pregnant were you at time of delivery?	___weeks ___no answer ___don't know ⌊was the baby premature (less than 37 weeks or 259 full days)? ___Yes ___No ___Don't know	___weeks ___no answer ___don't know ⌊was the baby premature (less than 37 weeks or 259 full days)? ___Yes ___No ___Don't know	___weeks ___no answer ___don't know ⌊was the baby premature (less than 37 weeks or 259 full days)? ___Yes ___No ___Don't know	___weeks ___no answer ___don't know ⌊was the baby premature (less than 37 weeks or 259 full days)? ___Yes ___No ___Don't know
Did you breastfeed this baby?	[1]yes⇒ # of weeks you breastfed this baby:___ [2] no [8] don't know [9] no answer	[1]yes⇒ # of weeks you breastfed this baby:___ [2] no [8] don't know [9] no answer	[1]yes⇒ # of weeks you breastfed this baby:___ [2] no [8] don't know [9] no answer	[1]yes⇒ # of weeks you breastfed this baby:___ [2] no [8] don't know [9] no answer
Does this child currently live with you, either part-time or full-time?	[1]Yes, full-time [2] Yes, part-time [3] No, reason:	[1]Yes, full-time [2] Yes, part-time [3] No, reason:	[1]Yes, full-time [2] Yes, part-time [3] No, reason:	[1]Yes, full-time [2] Yes, part-time [3] No, reason:

PART THREE. LIFESTYLE (We ask all women in this study about their lifestyles...)

Alcohol (First, some questions about alcohol... by a "drink", we mean one bottle/glass/can of beer, one glass of wine or one wine cooler, or one drink/highball/cocktail with 1 ounce of liquor)*(interviewer: you do not need to repeat the definition of a drink if read for "previous pregnancy" section)*

1. In the 12 MONTHS BEFORE THIS PREGNANCY, how often, on average, did you drink an alcoholic beverage? [1] Every day

[2] 4-6 times per week
[3] 2-3 times per week
[4] Once a week
[5] 2 to 3 times a month
[6] Once a month
[7] Less than once a month
[0] Not at all *(go to question 5)*
[8] Don't know *(go to question 2)*
[9] No answer *(go to question 2)*

Comments
_____
_____
_____

2. On the days you drank alcohol in the 12 MONTHS BEFORE THIS PREGNANCY , how many drinks per day did you usually have? _____*(enter average # drinks per day*)

3. In the 12 MONTHS BEFORE THIS PREGNANCY, how many times did you drink 5 or more alcoholic drinks on any one occasion? Your best guess is ok.

[1] Every day
[2] 4-6 times per week
[3] 2-3 times per week
[4] Once a week
[5] 2 to 3 times a month
[6] Once a month
[7] Less than once a month: how many times in past 12 months? _____
[0] Not at all *(go to question 4)*
[8] Don't know *(go to question 4)*
[9] No answer *(go to question 4)*

4. We ask all woman who have ever drank alcohol the following questions... (source: T-ACE)

T-ACE Score *(not read to participant)*

4a. How many drinks does it take to make you feel high? ___ drinks ___don't know ___no answer
(if definition of high is asked, say "in other words, start to feel the effects of alcohol, e.g. tipsy, lightheaded)"
___(score 2 for 3 or more drinks)
(score 0 for 2 or less drinks)

4b. Have people annoyed you by criticizing your drinking? [1]yes [2] no [8] don't know [9] no answer
___(score 1 for "yes")

4c. Have you ever felt you ought to cut down on your drinking? [1]yes [2] no [8] don't know [9] no answer
___(score 1 for "yes")

4d. Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? [1]yes [2]no
___(score 1 for "yes")

[8] don't know
[9] no answer
___Total T-ACE (add above scores)

5. DURING THIS PREGNANCY, how often, on average, have you drank an alcoholic beverage?

[1] Every day----------
[2] 4-6 times per week
[3] 2-3 times per week
[4] Once a week
[5] 2 to 3 times a month
[6] Once a month
[7] Less than once a month----------
[0] Not at all (go to question 10)
[8] Don't know
[9] No answer

| *If participant mentions only drank before*
| *knew was pregnant, still ask questions*
| *on frequency but check this box:* ☐
| *(not directly asked)*
| *Comments:* _____
_____
_____

6. Did you drink during this pregnancy but before you knew you were pregnant?
[1]Yes
[2] No
[8] Don't know
[9] No answer

7. On the days you drank alcohol DURING THIS PREGNANCY, how many drinks per day have you usually had?
_____*(enter average # drinks per day)*

8. DURING THIS PREGNANCY, how many times have you drank 5 or more alcoholic drinks on any one occasion? _____*# of times (best guess is ok)*

9. During which trimester(s) did you drink?
[1]1st trimester
[2] 2nd trimester
[3]3rd trimester
[4]1st and 2nd trimesters
[5]1st and 3rd trimesters
[6] 2nd and 3rd trimesters
[7] All trimesters
[8] Don't know
[9] No answer

Cigarette Smoking

10. Have you smoked at least 100 cigarettes in your entire life?
[1] Yes [2] No *(if "no", go to question 11)* [8] Don't know *(go to 11)* [9] no answer *(go to 11)*

11. In the 12 MONTHS BEFORE THIS PREGNANCY, how often, on average, did you smoke cigarettes?

[1] Every day
[2] 4-6 times per week
[3] 2-3 times per week
[4] Once a week
[5] Less than once a week___
[0] Not at all *(go to question 12)*
[8] Don't know *(go to 11a)*
[9] No answer *(go to 11a)*

⇒ 11a. On the days you smoked in the 12 months before this pregnancy, how many cigarettes did you usually smoke per day? _____*cigarettes per day (go to question 12)*
(one pack=25 cigarettes)

Comments: _____

12. Have you smoked at least one whole cigarette DURING THIS PREGNANCY?
[1]Yes *(go to question 13)*
[2] No *(go to question 15)*
[8] Don't know *(go to question 13)*
[9] No answer *(go to question 13)*

13. DURING THIS PREGNANCY, how often, on average, have you smoked cigarettes?

[1] Every day
[2] 4-6 times per week
[3] 2-3 times per week
[4] Once a week
[5] Less than once a week___
[8] Don't know *(go to 14)*
[9] No answer *(go to 14)*

⇒ On the days you smoked in this pregnancy, how many cigarettes have you usually smoked per day?
_____*cigarettes per day (go to question 14)*
(one pack=25 cigarettes)

If participant mentions only smoked before found out pregnant, ask frequency questions but check this box: ☐
(not directly asked)

Comments:
_____

14. IN THE PAST WEEK (7 days), how often, on average, have you smoked cigarettes?

[1] Every day
[2] 4-6 days in the last week
[3] 2-3 days in the last week
[4] Once in the last week
[0] Haven't smoked in past week
[8] Don't know
[9] No answer

⇒ On the days you smoked in the past 7 days, how many cigarettes have you usually smoked per day?
_____*cigarettes per day (one pack=25 cigarettes)*

Street Drugs

15. Did you use street drugs such as marijuana or cocaine in the 12 MONTHS BEFORE THIS PREGNANCY? [1] Yes [2] No *(go to question 16)* [8] Don't know *(go to 16)* [9] No answer *(go to 16)*

15a. If yes, which street drugs did you use in the 12 months before this pregnancy? *(check all that apply)*

__ Marijuana or Hashish (hash, pot, hash oil, hash putty)
__ Cocaine or crack (coke, rock)
__ Heroin (smack, horse)
__ Tranquilizers (downers, ludes)
__ Stimulants: amphetamines (uppers, speed, crystal)
__ Psychedelics/Hallucinogens: mushrooms, LSD/Acid, PCP/Angel Dust, Ecstasy
__ Inhalants: glue, gas, toluene, hairspray, other aerosols
__ Other (Specify)_____

15b. How often, on average, did you use street drugs during the 12 months before this pregnancy?

[1] Every day
[2] 4-6 days per week
[3] 2-3 days per week
[4] Once a week
[5] 2-3 times a month
[6] Once a month
[7] Less than once a month
[8] Don't know
[9] No answer

Comments:
_____

15c. In the past 12 months, have you used any street drugs intravenously, in other words, with a needle?
[1] Yes [2] No [8] Don't know [9] No answer

Have you used street drugs such as marijuana or cocaine DURING THIS PREGNANCY?
[1] Yes [2] No *(go to Part 4, page 14)* [8] Don't know *(go to Part 4)* [9] No answer *(go to Part 4)*

16a. If yes, which street drugs have you used during this pregnancy? *(check all that apply)*

__ Marijuana or Hashish (hash, pot, hashish oil, hashish putty)
__ Cocaine or crack (coke, rock)
__ Heroin (smack, horse)
__ Tranquilizers (downers, ludes)
__ Stimulants: amphetamines (uppers, speed, crystal)
__ Psychedelics/Hallucinogens: mushrooms, LSD/Acid, PCP/Angel Dust, Ecstasy
__ Inhalants: glue, gas, toluene, hairspray, other aerosols
__ Other (Specify)_____

16b. How often, on average, have you used street drugs during this pregnancy?

[1] Every day_____
[2] 4-6 days per week
[3] 2-3 days per week
[4] Once a week
[5] Less than once a week
[8] Don't know_____
[9] No answer

| check if only used drugs before knew pregnant: □
| (not directly asked)
| *Comments:*
_____

16c. During this pregnancy, have you used any street drugs intravenously, in other words, with a needle? [1] Yes [2] No [8] No answer [9] Don't know

PART FOUR. FOOD ACCESS
The next questions are about access to food and diet. (source: Health Canada, NPHS, 1996)

1. Thinking about the past 12 months, did your household ever run out of money to buy food?
[1] Yes [2] No [8] Don't know [9] No answer

2. In the past 12 months, has anyone in your household received food from a food bank, soup kitchen, or other charitable agency? [1] Yes [2] No [8] Don't know [9] No answer

3. Which of the following best describes the food situation in your household?
[1] Always enough food to eat
[2] Sometimes not enough food to eat
[3] Often not enough food to eat
[8] Don't know
[9] No answer

PART FIVE. DIET AND EXERCISE *=new questions

1*. During this pregnancy, how often, on average, have you included the following in your daily diet?

	Never	Rarely	Occasionally	Most of the Time	Always	Don't know	No Answer
a. Cow milk or or milk products or goat's milk? (e.g. cheese, yogurt)?	[1]	[2]	[3]	[4]		[5]	[8] [9]
b. Soy milk or soy products (e.g. tofu)?	[1]	[2]	[3]	[4]		[5]	[8] [9]
c. Coffee or Tea? (with caffeine)	[1]	[2]	[3]	[4]		[5]	[8] [9]
d. Herbal Teas?	[1]	[2]	[3]	[4]		[5]	[8] [9]
e. Soda Pop or Slurpees?	[1]	[2]	[3]	[4]		[5]	[8] [9]
f. Tap Water or Bottled Water?	[1]	[2]	[3]	[4]		[5]	[8] [9]
g. Grain products? (e.g. bread, rice, cereal, pasta)	[1]	[2]	[3]	[4]		[5]	[8] [9]
h. Vegetables or vegetable juices?	[1]	[2]	[3]	[4]		[5]	[8] [9]
i. Fruits or fruit juices?	[1]	[2]	[3]	[4]		[5]	[8] [9]
j. Meat or meat alternatives (e.g. beef, fish, pork, chicken, tofu, beans, nuts, seeds, eggs)	[1]	[2]	[3]	[4]		[5]	[8] [9]
k. Chocolate, chips, candy, or sweets	[1]	[2]	[3]	[4]		[5]	[8] [9]

2. Do you consider yourself vegetarian, in other words, do you avoid eating meat, fish, or poultry?
[1]Yes: for how many years or months have you avoided meat, fish, or poultry: _____years
[2] No _____months
[8] Don't know _____don't know
[9] No answer
_____no answer
source: Tough&Johnston, Colorectal Cancer Study

3*. During this pregnancy, how often, on average, have you...

	Never	Rarely	Occasionally	Most of the Time	Always	DK*	NA**
a. Skipped eating a morning meal (breakfast)?	[1]	[2]	[3]	[4]		[5]	[8] [9]
b. Skipped eating an afternoon meal (lunch)?	[1]	[2]	[3]	[4]		[5]	[8] [9]
c. Skipped eating an evening meal (dinner)?	[1]	[2]	[3]	[4]		[5]	[8] [9]

*DK=don't know; **NA= no answer

4*. Thinking back to JUST BEFORE YOU BECAME PREGNANT with this baby, would you say your weight was:
[1]Lower than it has usually been in most of your adult life⇒about how much lower?__lbs __kgs __dk __NA
[2]About the same as it has usually been in most of your adult life
[3]Higher than it has usually been in most of your adult life⇒about how much higher?__lbs __kgs __dk __NA
[8]Don't know
[9]No answer (*interviewer: enter average weight if range given, e.g. if 10-15 lbs, enter 12.5 pounds)*

5. During this pregnancy, how often, on average, have you exercised for 20 minutes or more without stopping?
[1] Every day
[2] 4-6 times per week
[3] 2-3 times per week
[4] Once a week
[5] Less than once a week
[0] Not at all
[8] Don't know
[9] No answer
interviewer: physical activity at work or home can apply here, as long as activity involves breathing being faster than normal and the activity is done for 20 minutes or more without stopping
(source: derived from Hawaii Healthy Start, PRAMS)

6. In the 12 months before this pregnancy began, how often, on average, did you exercise for 20 minutes or more without stopping?
[1] Every day
[2] 4-6 times per week
[3] 2-3 times per week
[4] Once a week
[5] Less than once a week
[0] Not at all
[8] Don't know
[9] No answer
interviewer: physical activity at work or home can apply here, as long as activity involves breathing being faster than normal and the activity is done for 20 minutes or more without stopping
(source: derived from Hawaii Healthy Start, PRAMS)

PART SIX. THOUGHTS AND EXPERIENCES
The next questions are about your thoughts, feelings, and life experiences.
Feelings about Pregnancy:
1. How happy are you to be pregnant at this time? (source: TNRT study)
[1] Not at all happy
[2] A little unhappy
[3] Neutral
[4] Happy
[5] Very happy
[8] I don't know
[9] No answer

2. Thinking back to JUST BEFORE YOU GOT PREGNANT, how did you feel about becoming pregnant? (chose the answer that best describes your feelings)
[1] I wanted to be pregnant earlier
[2] I wanted to be pregnant at a later point in time
[3] I wanted to be pregnant at that point in time
[4] I didn't want to be pregnant then or any time in the future
[8] I don't know
[9] No answer (source: Derived from Hawaii Healthy Start, PRAMS)

Self-Esteem: (source: Rosenberg, 1965,1979)
3. Please tell me if you strongly agree, agree, disagree, or strongly disagree with each of the following statements.

1	Strongly agree
2	Agree
3	Disagree
4	Strongly disagree
8	Don't know
9	No answer

Statement	#
On the whole, I am satisfied with myself.....	
At times, I think I am no good at all.....	
I feel that I have a number of good qualities.....	
I am able to do things as well as most other people.....	
I feel I do not have much to be proud of.....	
I certainly feel useless at times.....	
I feel that I'm a person of worth, at least on an equal plane with others.....	
I wish I could have more respect for myself.....	
All in all, I am inclined to feel that I am a failure.....	
I take a positive attitude toward myself.....	

interviewer: if participant absolutely insists on neutral, note this in column as a "7" and also ask another number they would chose if had to pick other than neutral...a neutral option should not be offered, and participants should be encouraged to pick SA, A, D, SD as otherwise the scale becomes ineligible)

Symptom Questionnaire: *Interviewer:* I am now going to read you a list of feelings people can have. Please tell me if the word describes how you have felt DURING THE PAST WEEK, INCLUDING TODAY. For example, the first word I will read is nervous: if you have felt nervous in the past week, including today, please say "yes". A few times you will have the choice of answering "true" or "false" instead of "yes" or "no". Do not think long before answering. If you would like me to explain or repeat a word, please let me know.* Sometimes the words will sound similar or the word "not" is used, so please listen as carefully as possible.

WORD	RESPONSE**		IF MEANING UNCLEAR	CODING (for study use only)			
	Yes	No		D	A	A-H	S
1. Nervous			Tense/uneasy		+		
2. Weary			Tired/fatigued	+			
3. Irritable			illtempered/cross			+	
4. Cheerful			happy	--			
5. Tense, tensed up			on edge		+		
6. Sad, blue			not happy	+			
7. Happy			cheerful/glad	--			
8. Frightened			scared		+		
9. Feeling calm			at ease/relaxed		--		
10. Feeling healthy			well/fit				--
11. Losing temper easily			angry/annoyed			+	
12. Feeling of NOT enough air	T	F	short of breath, panic				+
13. Feeling kind towards other people			nice, friendly			--	
14. Feeling fit			healthy, strong				--
15. Heavy arms or legs			no energy/weak				+
16. Feeling confident			sure/certain		--		
17. Feeling warm towards other people			nice, friendly			--	
18. Shaky			unstable/jittery		+		
19. NO pains anywhere	T	F	nothing hurts				--
20. Angry			mad/cross			+	
21. Arms and legs feel strong			energy/strong				--
22. Appetite poor			don't feel like eating				+
23. Feeling peaceful			quiet/at ease		--		
24. Feeling unworthy			not good enough	+			
25. Annoyed			angry/upset			+	
26. Feeling of rage			angry/mad			+	
27. Cannot enjoy yourself	T	F	no joy/happiness	+			
28. Tight head or neck			tense/stiff				+
29. Relaxed			calm/at ease		--		
30. Restless			can't sit still		+		
31. Feeling friendly			nice, warm			--	
32. Feeling of hate			dislike			+	
33. Choking feeling			gag/cant breathe				+

Y=YES [1] ; N=NO [2]; T=TRUE [1]; F=FALSE [2]; DK=DON'T KNOW [8]; NA=NO ANSWER [9]

WORD	RESPONSE**		IF MEANING UNCLEAR	CODING (for study use only)			
	Yes	No		D	A	A-H	S
34. Afraid			scared, fear		+		
35. Patient			don't feel rushed			--	
36. Scared			afraid/fear		+		
37. Furious			mad/angry			+	
38. Feeling charitable, forgiving			giving/generous/ helpful			--	
39. Feeling guilty			responsible/fault	+			
40. Feeling well			good/fine/fit	--			
41. Feeling of pressure in head or body			weight/force/ heaviness				+
42. Worried			concerned		+		
43. Contented			happy	--			
44. Weak arms or legs			no energy/tired				+

45. Feeling desperate, terrible			hopeless	+			
46. NO aches anywhere	T	F	nothing is sore				--
47. Thinking of death or dying			passing away	+			
48. Hot tempered			mad/upset			+	
49. Terrified			scared/afraid		+		
50. Feeling of courage			brave		--		
51. Enjoying yourself			happy	--			
52. Breathing difficult			gasp/no air				+
53. Parts of the body feel numb or tingling			frozen/tickly				+
54. Takes a long time to fall asleep			own opinion of "long time"		+		
55. Feeling hostile			harsh/unfriendly			+	
56. Infuriated			irate, engaged, really angry			+	
57. Heart beating fast or pounding			racing heart				+
58. Depressed			down,sad,blue	+			
59. Jumpy			restless/on edge		+		
60. Feeling a failure			not accomplish	+			
61. NOT interested in things	T	F	uninvolved	+			
62. Highly strung			wound up/wired		+		
63. CANNOT relax	T	F	not calm		+		
64. Panicky			not calm		+		
65. Pressure on head			tension/stress				+
66. Blaming yourself			guilt/at fault	+			
67. Thoughts of ending your life			suicidal thoughts	+			
68. Frightening thoughts			scary/upsetting		+		
69. Enraged			feel rage, anger			+	

Y=YES [1] ; N=NO [2]; T=TRUE [1]; F=FALSE [2]; DK=DON'T KNOW [8]; NA=NO ANSWER [9]

WORD	RESPONSE**		IF MEANING UNCLEAR	CODING (for study use only)			
	Yes	No		D	A	A-H	S
70. Irritated by other people			annoyed			+	
71. Looking forward to the future			optimistic/ hopeful	--			
72. Nauseated, sick to stomach			ill/flu like				+
73. Feeling that life is bad			sad,blue	+			
74. Upset bowels or stomach			ill/flu like/gas				+
75. Feeling inferior to others			others better	+			
76. Feeling useless			of no help	+			
77. Muscle pains			hurts				+
78. NO unpleasant feelings in head or body	T	F	head/body feels good/ok				--
79. Headaches			head hurts				+
80. Feel like attacking people			angry/hostile			+	
81. Shaking with anger			angry			+	
82. Mad			angry			+	
83. Feeling of goodwill			nice, kind			--	
84. Feel like crying			sad, blue	+			
85. Cramps			in knots/pain				+
86. Feeling that something bad will happen			something awful/ you don't want		+		
87. Wound up, uptight			tense/on edge		+		
88. Get angry quickly			mad quicktemper			+	
89. Self-confident			sure of self		--		
90. Resentful			offended/angry			+	
91. Feeling of hopelessness			despair/bleak	+			
92. Head pains			head hurts				+
SUBTOTAL***----------	-----	-------	----------				

--							
TOTAL (A + D + S + H)=							

*interviewer: all efforts should be taken to avoid using other words. If participant does not understand the meaning of 3 or more words, translation should be considered
**Y=YES [1] ; N=NO [2]; T=TRUE [1]; F=FALSE [2]; DK=DON'T KNOW [8]; NA=NO ANSWER [9]
***Interviewer: add up totals of yes responses to "+" and "-" in the A, D, S, H columns for questions 1-92. A "+" counts as +1, a "-" counts as -1

Read to participant: thank you! We realize that some of the words were similar. We have to ask all these words because the survey was made by someone else and can't be changed.
(Source: Robert Kellner, Symptom Questionnaire)

Family History and Life Events The next questions are about your life events and family...
1. In the past, have you ever had any of the following:
a. alcohol problems? [1] Yes [2] No [8] Don't know [9] No answer
b. drug problems? [1] Yes [2] No [8] Don't know [9] No answer
c. not having a job for a long time when you wanted to be working?* [1] Yes [2] No [8] Don't know [9] No answer
d. depression? [1] Yes [2] No [8] Don't know [9] No answer
e. suicidal thoughts or attempts? [1] Yes [2] No [8] Don't know [9] No answer

2. To the best of your knowledge, does any one in your immediate family (parents, sisters or brothers, grandparents) have a history of:
a. alcohol problems? [1] Yes [2] No [8] Don't know [9] No answer
b. drug problems? [1] Yes [2] No [8] Don't know [9] No answer
c. not having a job for a long time when they wanted to be working?* [1] Yes [2] No [8] Don't know [9] No answer
d. depression? [1] Yes [2] No [8] Don't know [9] No answer
e. suicidal thoughts or attempts? [1] Yes [2] No [8] Don't know [9] No answer

-**if participant asks "what is a long time?", ask them to think about what they consider a long time*
- interviewer: aunts, uncles, cousins don't apply here. Step or Adoptive parents, sisters, brothers, or grandparents count.
(source: new questions)

3. The next question is about things that may have happened to you in the past, or may be happening to you now. When we use the word parents, we also mean step-parents or foster-parents or any adult who was your legal guardian. To the best of your knowledge, do any of the following apply to you?

Interviewer: if participant answers "yes" to a question, follow up with the following questions and write answer in appropriate space after the response. (1) what was your age when this first happened or started happening? (2) On a scale of 1 to 5, where 1 is not at all stressful and 5 is very stressful, please tell me how stressful this event was for you at the time? (3) On a scale of 1 to 5, where 1 is not at all stressful, and 5 is very stressful, please tell me how stressful this event still is for you right now?

start then... now...		Age	Stress	Stress
a. You spent 2 weeks or more in a hospital?*	[1]Yes [2]No [8]DK [9]No answer	___	____	____
b. Your parents were separated?*	[1]Yes [2]No [8]DK [9]No answer	___	____	____
c. Your parents were divorced?*	[1]Yes [2]No [8]DK [9]No answer	___	____	____
d. One of your parents drank or used drugs so much that it caused problems for the family?*	[1]Yes [2]No [8]DK [9]No answer	___	____	____
e. One of your parents did not have a job for a long time when they wanted to be working?	[1]Yes [2]No [8]DK [9]No answer	___	____	____
f. You were bullied or harassed by others on a regular basis?	[1]Yes [2]No [8]DK [9]No answer	___	____	____
g. Your parents had frequent arguments	[1]Yes [2]No [8]DK [9]No answer	___	____	____
h. Your parents had violent arguments	[1]Yes [2]No [8]DK [9]No answer	___	____	____
i. Someone close to you unexpectedly died?	[1]Yes [2]No [8]DK [9]No answer	___	____	____

*source: Health Canada, NPHS, others new questions

4. On average, before age 17, how much did you feel that your father loved you and cared about you? If you had more than one father/step-father, or foster-father, please tell me and I will ask the question for each one:
(interviewer: step/foster father or other adult male who was legally responsible for participant also applies)
Where: 1=He did not love you or care for you at all and 5=He loved and cared for you very much
(interviewer: enter "8" for don't know and "9" for no answer)
Father#: 1. ___ 2. ___ 3. ___ 4. ___ 5. ___

5. On average, before age 17, how much did you feel that your mother loved you and cared about you? If you had more than one mother/step-mother, or foster-mother, please tell me and I will ask the question for each one: *(interviewer: step/foster mother or other adult female who was legally responsible for participant also applies)*
Where: 1=She did not love you or care for you at All and 5=She loved and cared for you very much
(interviewer: enter "8" for don't know and "9" for no answer)
Mother#: 1. ___ 2. ___ 3. ___ 4. ___ 5. ___ source: derived from Childhood Maltreatment Schedule, Briere J., Runtz M, 1990)

Abuse: Abuse can take many forms: physical, emotional (including psychological or verbal), sexual, financial (e.g. withholding or controlling money) or neglect. We ask all participants in this study about abuse in their lives. (*source: derived from domestic violence committee and CPNP)*

1. Have you ever seen or witnessed someone close to you be physically abused, emotionally abused, sexually abused, financially abused, or neglected?
[1] Yes [2] No *(go to question 2)* [8] Don't know *(go to Q2)* [9] No answer *(go to Q2)*
⇓*(interviewer: read each option)*

Which types?	How often have you witnessed this?		Happened to*	By Who?*	Has it stopped?**
__ physical	___	------	1=once	_____	_____ [1]yes[2]no[8]dk[9]na
__ emotional	___	|	2=rarely	_____	_____ [1]yes[2]no[8]dk[9]na
__ sexual ___		|	3=sometimes	_____	_____ [1]yes[2]no[8]dk[9]na
__ financial	___	|	4=often	_____	_____ [1]yes[2]no[8]dk[9]na
__ neglect ___	------		8=don't know	_____	_____ [1]yes[2]no[8]dk[9]na
			9=no answer		

*note to interviewer: if participant mentions abuse by partner, clarify if "ex" or "current" partner and write appropriate response under the "by who?" response category, e.g. "current husband", "ex-husband", "current partner", "ex-husband". DO NOT ASK NAMES, ONLY DESCRIBE RELATIONSHIP TO PARTICIPANT, E.G. "MOTHER, FRIEND, EX-PARTNER ETC...).
**interviewer: please indicate "yes"[1], "no"[2], "don't know",[8] or "no answer"[9]

2. Have you ever been physically abused, emotionally abused, sexually abused, financially abused, or neglected?
[1] Yes [2] No (go to Part 7) [8] Don't know (go to Part 7) [9] No answer (go to Part 7)
⇓*(interviewer: read each option*)

Which types?	How often?			By Who?	Age Started	Has Stopped?	Age Stopped
__ physical	___	------	1=once	_____	_____	[1]yes[2]no[8]dk[9]na	_____
__ emotional	___	|	2=rarely	_____	_____	[1]yes[2]no[8]dk[9]na	_____
__ sexual ___		|	3=sometimes	_____	_____	[1]yes[2]no[8]dk[9]na	_____
__ financial	___	|	4=often	_____	_____	[1]yes[2]no[8]dk[9]na	_____
__ neglect ___	------		8=don't know	_____	_____	[1]yes[2]no[8]dk[9]na	_____
			9=no answer				

(na if hasn't stopped)
*note to interviewer: if participant mentions abuse by partner, clarify if "ex" or "current" partner and write appropriate response under the "by who?" response category, e.g. "current husband", "ex-husband", "current partner", "ex-husband"

PART SEVEN: HOME

Housing:
1. What kind of housing are you currently living in (type of dwelling)?
[1] House
[2] Apartment
[3] Duplex/Four-plex
[4] Townhouse
[5] Institution: specify: _____
[6] Collective (group) dwelling (e.g. hotel, shelter, boarding house, colony) specify: _____
[7] other: Specify: _____*(interviewer: enter combinations of above here)*
[8] don't know
[9] no answer source: Health Canada, NPHS, 1996

2. Do you rent or own this dwelling (housing you are currently living in)?
[1] rent
[2] own
[3] other, specify: _____*(interviewer: enter combinations of above here)*
[8] don't know
[9] no answer source: derived from Health Canada, NPHS, 1996

People in Household:

3. Including yourself, how many people currently live in your household?_____
(people who live in your household on a part-time basis also count)*(do not enter pets)*

If you live with someone else, please tell me their age, relationship to you (i.e. is the person your spouse, partner, child, mother-in-law, friend etc...), and if your household is their main residence (i.e. is this where they live most of the time)?

Other Resident#* √ if applies	Age?**	What is their Relationship to You?**	Is your Household their Main Residence?**
__ Other resident#1:	Age ____	Relationship to you: _____	[1] Yes [2] No
__ Other resident#2	Age ____	Relationship to you: _____	[1] Yes [2] No
__ Other resident#3	Age ____	Relationship to you: _____	[1] Yes [2] No
__ Other resident#4	Age ____	Relationship to you: _____	[1] Yes [2] No
__ Other resident#5	Age ____	Relationship to you: _____	[1] Yes [2] No
__ Other resident#6	Age ____	Relationship to you: _____	[1] Yes [2] No
__ Other resident#7	Age ____	Relationship to you: _____	[1] Yes [2] No
__ Other resident#8	Age ____	Relationship to you: _____	[1] Yes [2] No
__ Other resident#9	Age ____	Relationship to you: _____	[1] Yes [2] No
__ Other resident#10	Age ____	Relationship to you: _____	[1] Yes [2] No

*check if applies **enter "dk" if don't know, "na" if no answer

Other, specify: _____
source: TNRT

Home ETS:

4. Which best describes the way smoking is handled in your home? Is Smoking:
(check one answer only)
[1] not allowed in the home *(interviewer: if smoking only allowed outside of house, check option #1)*
[2] not allowed when children are present
[3] confined to certain areas of the home
[4] permitted any where
[8] don't know
[9] no answer

source: TNRT STUDY (Tough et al)

PART EIGHT. SPOUSE/PARTNER

1. Do you currently have a spouse or partner?
[1]Yes (go to question 2) [8] Don't know
[2] No (go to question 3) [9] No answer

2. Is the baby's father your current partner?
[1]Yes
[2] No *(ask questions 4-13 for each partner and write "baby's father" or "current partner" to correspond with who the answer refers to)*
[8] Don't know
[9] No answer

3. What is your current marital status? At present are you...
[1] Single (Never married)
[2] Married
[3] Common Law/Living with Partner
[4] Divorced
[5] Separated
[6] Widowed
[8] Don't know
[9] No answer

source: Health Canada, NPHS, 1996

	Partner	Baby's father (if different)
4. How old is your partner?	____age in years *(best guess ok)*	___age in years
	____don't know	___don't know
	____no answer	___no answer

5. What is your partner's highest grade or level of education?

[1] Elementary (Grades 1-6)
[2] Junior High (Grades 7-9)
[3] Some High School (Grades 10-11)
[4] Graduated High School

[5] Some Trade, Technical, Vocational School or Business/Community College (e.g. SAIT, Devry)
[6] Some University (e.g. University of Calgary)
[7] Completed Trade, Technical, Vocational School or Business/Community College (e.g. Sait, Devry)
[8] Completed University Undergraduate Degree (e.g. B.A., B.SC., LL.B.)
[9] Completed Post-Graduate Degree (e.g. M.A., M.SC., M.ED., M.D., D.D.S., D.M.D., D.V.M., O.D., PH.D., D.Sc., D.ED.)
[10] Other, specify: _____
[88] Don't know
[99] No answer

If baby's father is different than current partner, write baby's father's education (code) here: _____
Source: derived from Health Canada, NPHS, 1996)

6. Which of the following best describes your partner's MAIN activity (check one only)? Is he mainly...
[1] Working at a job or business (go to question 7)
[2] A homemaker
[3] Looking for work
[4] On paid paternity/parental leave
[5] A student ⇒ go to question 9.
[6] Other, specify: _____*
[8] Don't know
[9] No answer

If baby's father is different than current partner, write baby's father's activity (code) here: _____

**interviewer: enter combinations of above here, circle MAIN activity when enter combination (e.g. 4 and 5)*
source: derived from Health Canada, NPHS (took out retired and added in on paid paternity leave)

7. What is your partner's occupation (e.g. lawyer, farmer, teacher)? _____
-If baby's father is different than current partner, write baby's father's occupation (code) here: _____

8. How many hours per week does your partner usually work? _____(hours/week) (or "don't know)
-If baby's father is different than current partner, write baby's father's hours/week (code) here: _____

9. At the present time, does your partner smoke cigarettes:
[1] Every day?
[2] Occasionally?
[3] Not at all?
[8] Don't know
[9] No answer
If baby's father is different than current partner, write baby's father's smoking status (code) here: _____

10. At the present time, how often, on average, does your partner drink alcoholic beverage(s)?
[1] Every day
[2] 4-6 times per week
[3] 2-3 times per week
[4] Once a week
[5] 2 to 3 times a month
[6] Once a month
[7] Less than once a month
[0] Not at all (go to question 12)
[8] Don't know (go to question 11)
[9] No answer (go to question 11)
If baby's father is different than current partner, write baby's father's alcohol use (code) here: _____

11. On the days your partner drinks alcohol, how many drinks per day does he usually have? _____*(enter average # drinks per day or "don't know")*
- If baby's father is different than current partner, write baby's father's drinks/day (code) here: _____

Father's Feelings about Pregnancy:
12. How happy do you think your partner is that you are pregnant at this time?
[1] Not at all happy
[2] A little unhappy
[3] No opinion,
[4] Happy
[5] Very happy

[6] He doesn't know I'm pregnant
[8] I don't know how he feels
[9] No answer
- If baby's father is different than current partner, write baby's father's happiness (code) here: _____
source: TNRT study

13. Thinking back to JUST BEFORE YOU GOT PREGNANT, how do you think your partner felt about you becoming pregnant? (chose the answer that best describes his feelings)
[1] He wanted me to be pregnant earlier
[2] He wanted me to be pregnant at a later point in time
[3] He wanted me to be pregnant at that point in time
[4] He didn't want me to be pregnant then or any time in the future
[8] I don't know how he felt
[9] No answer (source: Derived from Hawaii Healthy Start, PRAMS)

If baby's father is different than current partner, write baby's father's timing feelings (code) here: _____
source: Hawaii Healthy Start, PRAMS

Spouse/Partner Relationship:
Interviewer: if participant does not have current partner, go to Part Nine (page 27)

14. About how long have you been with your current partner?
___years or ___months or __don't know ___no answer

15. In general, how would you describe the relationship with your partner, would you say...
[1] A lot of tension [2] Some tension [3] No tension [8] Don't know [9] No answer

16. Do you and your partner work out arguments with:
[1] Great difficulty [2] Some difficulty [3] No difficulty [8] Don't know [9] No answer

(interviewer: if participant mentions that does not argue with partner, ask them to think about how much difficulty not arguing causes the relationship, i.e. "would you say that not having arguments with your partner creates great difficulty, some difficulty, or no difficulty in your relationship")
source: WAST, Brown et al, Fam Med 1996; 28(6):422-8:426

PART NINE. COMMUNITY AND SOCIAL SUPPORT
Social Support Index
1. Please tell me if you Strongly Agree, Agree, are Neutral, Disagree, or Strongly disagree with each of the following statements about your community or family. Please think about your own community, friends, or family when answering these questions (interviewer enter: strongly agree=4, agree=3, neutral=2, disagree=1, strongly disagree=0, don't know=8, no answer=9).

a. If I had an emergency, even people I do not know in this community would be willing to help___
b. I feel good about myself when I sacrifice and give time and energy to members of my family___
c. The things I do for members of my family and the things they do for me make me feel part of this very important group ___
d. People here know they can get help from the community if they are in trouble___
e. I have friends who let me know they value who I am and what I can do___
f. People can depend on each other in this community___
g. Members of my family seldom listen to my problems or concerns; I usually feel criticized___
h. My friends in this community are part of my every day activities___
i. There are times when family members do things that make other members unhappy___
j. I need to be very careful how much I do for my friends because they take advantage of me___
k. Living in this community gives me a secure feeling___
l. The members of my family make an effort to show their love and affection for me___
m. There is a feeling in this community that people should not get too friendly with each other___
n. This is not a very good community to bring children up in___
o. I feel secure that I am as important to my friends as they are to me___
p. I have some very close friends outside the family who I know really care for me and love me___
q. Member(s) of my family do not seem to understand me; I feel taken for granted___

source: Social Support Index, McCubbin, Patterson, Glynn (SD=0, D=1, N=2, A=3, SA=4)
Network Orientation (Source: Network Orientation Scale, Vaux, Burda, Stewart)
1. I will now read a list of statements concerning relationships with other people. Please tell me if you Strongly Agree, Agree, Disagree, or Strongly Disagree with each statement. In other words, the answers you can chose from are exactly like the last question, except there is no "neutral" option.

Interviewer: enter: strongly agree=1, agree=2, disagree=3, strongly disagree=4, don't know=8, no answer=9
a. Sometimes is it necessary to talk to someone about your problems ___
b. Friends often have good advice to give ___
c. You have to be careful who you tell personal things to ___
d. I often get useful information from other people ___
e. People should keep their problems to themselves ___
f. It's easy for me to talk about personal and private matters ___
g. In the past, friends have really helped me out when I've had a problem ___
h. You can never trust people to keep a secret ___
i. When a person gets upset, they should talk it over with a friend ___
j. Other people never understand my problems ___
k. Almost everyone knows someone they can trust with a personal secret ___
l. If you can't figure out your problems, nobody can ___
m. In the past, I have rarely found other people's opinions helped when I have a problem ___
n. It really helps when you are angry to tell a friend what happened ___
o. Some things are too personal to talk to anyone about ___
p. It's fairly easy to tell who you can trust, and you who can't ___
q. In the past, I have been hurt by people I confided in (e.g. trusted telling them something private) ___
r. If you confide (put trust in) other people, they will take advantage of you ___
s. It's okay to ask favors of people ___
t. Even if I need something, I would hesitate to borrow it from someone ___

interviewer: if participant insists on a "neutral" answer, enter 7, and ask them if had to chose what they would chose. Enter the number they select when have to chose, and note that would have preferred "neutral" option, however. Do not offer neutral option.

Behaviours of Friends

2. Of the people you see socially, how many smoke cigarettes?
[1] None smoke cigarettes
[2] A few smoke cigarettes
[3] Most or all smoke cigarettes
[8] Don't know
[9] No answer
source: Health Canada, NPHS, 1996

3. Of the people you see socially, how many would you say drink too much alcohol?
[1] None
[2] A few
[3] Most or all
[8] Don't know
[9] No answer
source: Health Canada, NPHS, 1996

PART TEN. BEFORE YOU GO...

Before you go, we would like to ask you some background questions about yourself. Your answers are confidential. We use this information to compare groups of people in this study (e.g. age, marital status), not specific individuals, and to describe the participants in this study.

Age:

1. What is your birth date? month _____ day____ year_____ ___don't know ___no answer

Work Status:

2. Which of the following best describes your MAIN activity (check one answer only)? Are you mainly...

[1] Working at a job or business (either part-time, full-time, or casual)? ⇒ go to question 3.
[2] A homemaker
[3] Looking for work
[4] On paid maternity leave
[5] A student ⇒ go to question 6
[6] Other, specify: _____*
[8] Don't know
[9] No answer

*interviewer: enter combinations of above here, circle MAIN activity when enter combination (e.g. 2 and 5)
source: derived from Health Canada, NPHS (took out retired and added in on paid maternity leave)

Occupation:
3. What is your occupation (e.g. lawyer, farmer, teacher)? _____

Work Hours:
4. How many hours per week do you usually work? _____(hours/week) ___don't know ___no answer
source: Health Canada, NPHS, 1996

5. Which of the following best describes the hours you usually work (check one only)...
[1] Regular day time schedule?
[2] Regular afternoon or evening schedule?
[3] Regular night shift?
[4] Rotating shift (one that changes periodically)
[5] Other, specify: _____ (interviewer: if there is a combination of
[8] Don't know the above #4 should normally apply)
[9] No answer

source: Health Canada, NPHS, 1996
Education:
6. What is the highest level of education that you have attained (completed)?
[1] Elementary (Grades 1-6)
[2] Junior High (Grades 7-9)
[3] Some High School (Grades 10-11)
[4] Graduated High School
[5] Some Trade, Technical, Vocational School or Business/Community College (e.g. SAIT, Devry)
[6] Some University (e.g. University of Calgary)
[7] Completed Trade, Technical, Vocational School or Business/Community College (e.g. Sait, Devry)
[8] Completed University Undergraduate Degree (e.g. B.A., B.SC., LL.B.)
[9] Completed Post-Graduate Degree (e.g. M.A., M.SC., M.ED., M.D., D.D.S., D.M.D., D.V.M., O.D., PH.D., D.Sc., D.ED.)
[10] Other, specify: _____
[88] Don't know
[99] No answer
Source: derived from Health Canada, NPHS, 1996)

Income:
7. What is your Postal Code _____ don't know ___ no answer___

8. What is the total income, before taxes and deductions, of all household members from all sources in the past 12 months (you're best guess is ok)? Was the total household income:
[1] Less than $10,000
[2] $10,000-$19,999
[3] $20,000-$29,999
[4] $30,000-$39,999
[5] $40,000-$49,999
[6] $50,000-$59,999
[7] $60,000-$69,999
[8] $70,000-$79,999
[9] $80,000-$89,999
[10]$90,000-$99,999
[11] $100,000 or more
[88] Don't know
[99] I prefer not to answer this question
source: derived from Health Canada, NPHS, 1996

Calgary Residency
9. How long have you lived in Calgary, or a surrounding area? *probe if necessary:* If you live near Calgary, but not within the city limits, the time you have lived in an area surrounding Calgary also counts.
___years or ___months ___don't know ___no answer

interviewer: if participant has moved from and back to Calgary, enter the total number of years they have lived in Calgary or a surrounding area (e.g. Airdrie, Cochrane, Didsbury, Balzac, Beiseker, Okotoks, Strathmore)
Ethnicity:
10. What country were you born in?
[1] Canada
[2] Other, *specify:* _____ ⇒ How long have you lived in Canada? ___ years ___months
[8] Don't know ___ don't know
[9] No answer ___ no answer
source: derived from Health Canada, NPHS, 1996

11. How would you best describe your ethnic origin (race)?
[1] African North American/Black
[2] Caucasian/White (e.g. English, French, German, Irish, Polish, Scottish, Ukrainian)
[3] Chinese
[4] Filipino
[5] Greek
[6] Italian
[7] Japanese
[8] Korean
[9] Latin American (e.g. Brazilian, Chilean, Mexican)
[10 Native/Aboriginal Peoples of North America (First Nations, North American Indian, Metis, Inuit)
[11] South Asian (e.g. East Indian, Pakistani, Punjabi, Sri Lankan)
[12] South East Asian (e.g. Cambodian, Indonesian, Laotian, Vietnamese)
[13]West Asian/Arab (e.g. Armenian, Egyptian, Iranian, Lebanese, Moroccan)
[14] Other, specify _____
[88] Don't know
[99] No answer
source: derived from Health Canada, NPHS, 1996

Main Language Spoken at Home:
12. What language do you mainly speak at home (e.g. English, Punjabi, Italian, Cantonese)? _____ *(list one language only)*

Here Through Maternity
Every pregnant woman in Calgary receives a free copy of a book called "From Here through Maternity".

(*if Participant states that they have already received the book, go to* "CONTACT INFORMATION")

This book is about pregnancy and pregnancy resources in Calgary. When you go in for your first visit with your prenatal doctor, you should make sure you get a copy of this book. If you would like a copy of this book sooner, you should talk to your doctor or community health centre.

Contact Information Study ID: _____
We find it helpful to ask participants in the study how we can reach them for study purposes:
1. Is there a certain time of the day that you preferred to be called at? _____
2. Is there a certain day of the week that you preferred to be called on? _____
3. Is it ok if we leave a message with another person or an answering machine at the numbers we have listed for you (interviewer: read numbers), that is, if we call and you are not home? We never leave a message unless we have your permission, the only message I would leave is my first name and telephone number).
___yes, a member of the study team can leave a message at these numbers
___no: specify: _____

Thank You and follow-up
That concludes the questionnaire, thank you very much! Just a reminder that it is very important that you contact you medical doctors if you have any questions or concerns.

Do you want any phone numbers for agencies that you can contact for emotional support?
(if requested, the phone numbers are as follows:
The Crisis Line (Distress Centre) at 266-1605
Calgary Counselling Centre at 265-4980
Perinatal Bereavement Counselling Centre at 670-2248
Caring Beyond at 294-1131.

Just as a reminder, we ask that you put the sample collection kit in your hospital bag, if you haven't done so already.

THANK YOU AGAIN, DO YOU HAVE ANY QUESTIONS OR COMMENTS? (enter on next page)

B.2. Biomarker in Meconium and Child Development

B.2.1. Child History Form

Child's Name	Male	Female

Referral Information:

Do you have any other concerns that you would like us to address?
Do you and your partner share the same concerns?

Medical Information:

Does your child have any medical conditions or concerns that we should be aware of? If yes please explain:		
When did your child last see a Family Physician or Pediatrician for a check-up?		
Are your child's immunizations up-to-date?	Yes	No
Does your child have any allergies? (drug, food, pollens etc)	Yes	No
If yes, please list:		
Is your child presently on any medication(s)?	Yes	No
If yes, please list:		
Has your child ever suffered form frequent ear infections?	Yes	No
If yes, when?		
Has your child had a hearing test?	Yes	No
If yes, who tested? / When?	Results	
Do you currently have concerns regarding your child's hearing?		

Has your child had a vision test?		Yes	No
If yes, who tested?	When?	Results	
Do you currently have concerns regarding your child's vision?			
Does your child receive any of the following services?			
Speech/language		Yes	No
If yes, name of therapist:			
Occupational Therapy		Yes	No
If yes, name of therapist:			
Physiotherapy		Yes	No
If yes, name of therapist:			
Other therapies or interventions?		Yes	No
If yes, please describe: Who are the therapists involved:			

Other therapists or Agencies:

Are there other therapies or community agencies currently involved with your child?	Yes	No
If yes, please record agency, therapist's name and phone #		
Have any therapists or community agencies been involved with your child in the past?	Yes	No
If yes, please record agency, therapist's name and phone #		

Household Composition: Please list all members of current household – (adults and children)

Name	Sex	Date of Birth	Relationship to Child	Grade/Schooling Completed

Are there any immediate family members not living in the home?	Yes	No
If yes, list name, sex, age and relationship to child:		
What is the main language spoken at home? Indicate other languages that are sometimes used:		

Family History: Indicate with a check if any of the items below have occurred

	Child's Biological Mother	Child's Biological Father	Child's Brother	Child's Sister	Other(s) Specify
Daydreams					
Hyperactivity					
Trouble reading					
Trouble with arithmetic					
Trouble with writing					
Trouble with spelling					
Speech problems					
Kept back in school					
Behaviour problems as child					
Trouble as a teenager					
Depression					
Other mental illness					
Significant health problem					
Drinking or drug problem					

Pregnancy and Birth History:

Have you had any previous miscarriages?	Yes	No
Did you take any medications/drugs during this pregnancy?	Yes	No
If yes, please explain:		
Did you drink alcohol before you knew you were pregnant or during your pregnancy?	Yes	No
If yes, how much and how frequently?		
Did you use tobacco during your pregnancy?	Yes	No
If yes, how much and how frequently?		
Did you experience any problems during your pregnancy or birth of this child (bleeding, injuries, infections or other health concerns)?	Yes	No
If yes, please explain:		
Child's birth weight:		
Was your child born prematurely?	Yes	No
If yes, please explain:		
Did your child experience any difficulties either during birth or following the birth?	Yes	No
If yes, please explain		

Developmental History: Please complete the following Developmental History to the best of your recollection.

Rolled over from back to stomach, at _____ months	Pulled self to sitting position, at _____ months
Crawled at _____ months	Walked unassisted, at _____ months
Bladder trained: Day time at _____years Night time at _____years	Bowel trained, at _____years
Said first meaningful word(s) at _____months. What were they?	
Talked in short phrases, at _____ months.	
Talked in sentences, at _____ months.	

Fine Motor

Does your child like to draw or colour?	Yes	No

Activities of Daily Living

Do you have concerns with your child's behaviour at mealtimes (eg leaving the table)?	Yes	No
Is there significant family stress at mealtimes?	Yes	No
Does your child eat food from all food groups?	Yes	No
Are you concerned about your child's food intake or weight?	Yes	No
Will your child willingly try new foods?	Yes	No
Are there certain textures that your child refuses to eat?	Yes	No
Does your child need to have foods prepared or presented in a certain way to eat them?	Yes	No
Does your child eat with utensils?	Yes	No

Speech/Language Development

Does your child have difficulty saying words clearly/talking clearly?	Yes	No
Do others understand what your child says to them?	Yes	No
Is your child able to follow more than 1 direction at a time?	Yes	No
Does your child have difficulty remembering what was said to him/her?	Yes	No
Do you feel your child has speech/language delays?	Yes	No

Social/Emotional

When your child has free time at home, what do they choose to do?		
Does your child like to play with a variety of toys?	Yes	No
Does your child ever play with a toy in a way that is different from what you would expect?	Yes	No
Does your child engage in pretend play?	Yes	No
If you change the order of the toys, how does your child react?		
Can you join in your child's play?	Yes	No
Does your child prefer to play alone (solitary play)?	Yes	No
Does your child prefer to be around other children but play by themselves (parallel play)?	Yes	No
Does your child prefer to play with other children?	Yes	No
Will your child attempt to engage other children in his/her play?	Yes	No
Does your child prefer to play with children their own age?	Yes	No
Does your child prefer to play with younger children?	Yes	No
Does your child prefer to play with older children?	Yes	No
Does your child have a special friend(s)?	Yes	No
Does your child use eye contact when interacting with others?	Yes	No

Behaviours:

Does your child engage in certain behaviours that seem unusual to you or that you are concerned about?	Yes	No
Does your child have difficulty with changes in activity, routine or environment?	Yes	No
Does your child have any unusual routines or rituals?	Yes	No
Does your child have any fascinations, or unusual or intense interests in objects, toys or topics?	Yes	No
If yes, please explain:		
Does your child have any sensitivity to touch, noise, crowds, light, fast movement or being off the ground?	Yes	No
Is your child aggressive?	Yes	No
Do you often have to discipline your child?	Yes	No
Do you and your partner have similar approaches to discipline?	Yes	No

Please list you child's weaknesses:
Please list your child's strengths:
Is there any other information you feel we should know?

Thank you for your time in completing this questionnaire. The information is very useful in helping us understand your child better.

B.2.2. Pediatric Assessment Form

Note: Formatting of this form has been modified so that it meets the page restrictions of the thesis.

Child's Name: _____ Accompanied by: _____ Date: _____
Study ID#: _____ ACH #: _____ DOB : ____ Age: _____
Doctors: 1 (GP) _____ 2) (Pediatrician) _____

1. Present Parental Concerns
1.1

1.2

1.3

1.4

2. Nurturance: any concerns from Nurturance Inventory? _____Yes _____No

3. Developmental Review
3.1 Gross Motor Milestones: ___Roll ___Sit ___Crawl ___Walk
3.2 Gross Motor Now: ___Walk ___Stairs ___Alt Stairs
___Jump ___Hop ___Climb ___Coordinated

3.3 Fine Motor: ___Object Transfer ___Pincer ___Feed Self
___Utensil Use ___Pencil Grasp ___Coloring
___Scissors ___Dress Self ___Buttons ___Zippers
___Tie Shoes ___Handedness
___Sensory Aversion:
___Oral-Motor Difficulty:

3.4 Speech-Language Milestones: ___1st Words ___2 word Sentences
Coo/babble: ___Expressive:
Smile: ___Receptive:
Resp to Name: ___Dysfluency:
3.5 Speech-Language Now:
3.6 Cognitive: _____Alphabet _____Colors _____Numbers
3.7 Social Skills: ___Cuddles as Infant ___Seeks Comfort ___Guilt ___Friends ___Best Friend___Eye Contact:
3.8 Play: _____Imaginative Play _____Parallel Play _____Play Concerns
3.9 Toileting:Trained for Urine at_____; For Stool at _____.
_____Enuresis _____Encopresis _____Odd Toileting Behavior
3.10 Sleep: ____Initiation (time) ____Waking (time)____Naps_____24 hr total
3.11 _____Neuro Regression _____Seizures _____Absence Seizures ____Other Hard Neurological

3.12 Temperament:

4. Health Status, Co-morbidities and Pregnancy History
4.1 Maternal Co-morbidities:

4.2 Lifestyle
Did you drink alcohol during your pregnancy with this child?
_____Yes _____ No _____Don't Know
Did you drink alcohol during this pregnancy but before you knew you were pregnant?
_____Yes _____ No _____ Don't Know
Did you drink 5 or more drinks on any occasion prior to pregnancy recognition?
_____Yes _____ No _____Don't Know
On how many occasions? _____

Each of the following questions about cigarette, alcohol, and street drug use is repeated for each of the timeframes (i.e., prenatal, perinatal, postnatal, in the past year). Please enter responses in the Table above (Please Note: The Table did not fit within the page format for the thesis and was removed)
Please use the following routes
Prenatal – In the year prior to the pregnancy with this child did you:
Perinatal - During the pregnancy of your child in the study did you:
Postnatal - Following the delivery of your child in the study did you:
In the past year have you:

CIGARETTES (Please enter responses in table)
Smoke at least one whole cigarette? How many times per week?
iii. On the days you smoked, how many cigarettes did you usually smoke per day? _____(enter average # cigarettes per day)(1 pack=25 cigs)

ALCOHOL (Please enter responses in table)
Next, some questions about alcohol... by a "drink", we mean one bottle/glass/can of beer,
one glass of wine or one wine cooler, or one drink/highball/cocktail with 1 ounce of liquor.
Drink an alcoholic beverage? How many days per week?
On the days you drank alcohol, how many drinks per day did you usually have? By a "drink", we mean one bottle/glass/can of beer, one glass of wine or one wine cooler, or one drink/highball/cocktail with 1 ounce of liquor)

STREET DRUGS (Please enter responses in table)
Use street drugs such as marijuana or cocaine? How often?
ii. Which street drugs did you use? (check all that apply)
__ Marijuana or Hashish (hash, pot, hash oil, hash putty)
__ Cocaine or crack (coke, rock)
__ Heroin (smack, horse)
__ Tranquilizers (downers, ludes)
__ Stimulants: amphetamines (uppers, speed, crystal)
__ Psychedelics/Hallucinogens: mushrooms, LSD/Acid, PCP/Angel Dust, Ecstasy
__ Inhalants: glue, gas, toluene, hairspray, other aerosols
__ Other (Specify)_____

MEDICATION
Use any prescription medications, or CAMs? Types
1. 5.
2. 6.
3. 7.
4. 8.

4.3 Past Medical History:
4.3.1 Pregnancy: _____GDM _____HT _____Fever/ID _____Bleeding
Other:
4.3.2 Birth: EGA:_____wks Birth Type:__SVD __AugVD __C/S
Bwt_____gm Apgars: ____, ____
Resuscitation:
Complications: NICU:
4.3.3 Perinatal: ___Jaundice (Day) ___Wt Gain ___Feeding Pblm
4.3.4 Breast Feeding:
Problems:
Duration:
Formula Use:
4.3.5 Nutrition:
Introduction of Solids:
Introduction of Milk:
4.3.6 Current Diet:
Milk amount
Juice
Meat
Fruits and Vegetables

Starch

4.3.7 Medical Problems:
4.3.8 Hospitalizations:
4.3.9 Surgeries:
4.3.10 Accidents:
4.3.11 Head Trauma:
4.3.12 Allergies:
4.3.13 Immunizations (RA to copy from immunization record):
4.3.14 Medications:
4.3.15 CAMs:

4.4 Investigations to Date:

4.4.1 Metabolic
4.4.2 Genetic:
4.4.3 Neuroimaging:
4.4.4 EEG:
4.4.5 Audiology: Do you feel that your child hears well?
4.4.6 Ophthalmology: Do you feel that you child sees well?
4.4.7 Other:
4.4.8 Consultations:

4.5 Interventions to Date:

4.5.1 Speech-Language:
4.5.2 OT:
4.5.3 PT:

5. Family History

5.1 Social Assistance:
5.2 Psycho-Social Support:
5.3 Discipline:
5.4 History of Maltreatment:
5.5 Consanguinity:
5.6 Pregnancy Losses:
5.7 LD:
5.8 Attention:
5.9 Finished High School?
5.10 Autism/PDD/Odd:
5.11 Other Psychiatric:
5.12 Other Genetic:

6. Review of Systems:

7. Physical Examination:

Wt: _____kg (%) BP: _____ IC: _____cm (+/- SD)
Ht: _____cm (%) HR: _____ OC: _____cm (+/- SD)
HC: _____cm (%) RR: _____ R PFL: _____cm (+/- SD)
L PFL: _____cm (+/- SD
FAS Lip : ___/5 FAS Philtrum: ___/5

H+N: ___RTM ___LTM ___PERL ___EOM ___Cov/UncovX2 ___FundiX2 ___Orophar
_____Palate ____NaresX2 ____LN ____Thyroid

Pulm: ____A/E to Bases _____Adventitial

CVS: ____Precordium _____Apex ____Pulses _____BF Delay____Heart Sounds ____Murmur ____Radiating :_
Bruits: _____ Cranial _____Neck _____Renal

GI: ___BS ___Soft ___Nontender ___HSM ___Mass ___Stool ___Anus

GU: ___Anatomy _____Testes _____SMR Testes _____SMR Pns _____SMRAxHr

MSK: ___Power _____Tone _____Gait _____Tandem Gait___Spine ____NTD

Neuro: DTR	___L Bi	___R Bi	____Plantars	____Fine Motor
	___L Tri	___R Tri	____Clonus	____Motor Ovrflw
	___L Knee	___R Knee	____Cerebellar	____Rhomberg
	___L Ankle	___R Ankle	____Dysdiadok	____Other:

Derm: Direct Inspection: Wood's Lamp:

8. Physician Summary/Problem List:
1.

2.

3.

4.

9. Recommendations:
1.

2.

3.

4.

B.2.3. Assessments Used at Time of Follow Up

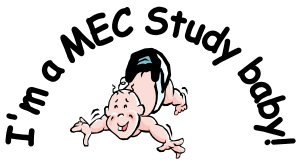
Table B2.1. Tests used at 24-Month Assessments.

24 Month Assessment			
Instrument	**Domains Assessed**	**Administration**	**Time (hours)***
BSID-II	Cognitive and motor development	Psychologist	1.2
Home Screening Questionnaire	Assesses family environment, parent-child relationships and factors that impact child development	Survey	0.3
ABAS	Assesses social and personal adaptability	Survey	0.6
Nurturance Inventory	Measures the child rearing practices of women with children between 2 to 11 years old	Pediatrician	0.15
Carey Temperament Scale	Assesses temperament of child and resulting behaviour and behaviour problems	Survey	0.4
Child Behavior Checklist	Parents' rating of child's problems, disabilities, concerns and strengths	Survey	0.3
Weschler Abbreviated Screening Intelligence	Measures intelligence	Psychologist	1.0
Parenting Satisfaction Survey	Assesses parent's attitudes with satisfaction of spouse/ex-spouse parenting performance, parent-child relationship and their parenting performance	Survey	0.3
Family Assessment Device	Assesses healthy and unhealthy family functioning	Survey	0.2
Total Time			4.5

*Time in hours for the psychology assessor to administer and score the test or score a standardized assessment.

B.2.4. Sample Psychology Report

Alberta Children's Hospital
Decision Support Research Team
Child, Adolescent, and Women's Health



Name:
Date of Birth:
Health Record Number:
Date of Visit:
NAME participated in a psychology assessment that was part of the 2 year developmental follow-up for the Meconium Study (Dr. Suzanne Tough, Principal Investigator).

The assessment included:
Bayley Scales of Infant Development, 2nd Edition (Mental Scale, Motor Scale, & Behavior Rating Scale)
Adaptive Behavior Assessment System: Second Edition
Child Behavior Checklist 1 ½ - 5 and Language Development Survey, and
Temperament and Atypical Behavior Scale

BEHAVIOUR OBSERVATIONS
NAME's performance on the measure of cognitive development was within normal limits. Her/HIS motor development was assessed as falling within the normal range. Based on parent report, NAME's vocabulary development and phrase length were within normal limits.

A parent questionnaire showed that NAME's general adaptive functioning was in the ---range. These results suggest that in HIS/HER everyday environment at home and in the community, NAME is showing adaptive behaviours that are within age expectancies.

The two behavioural questionnaires showed no major problems with behaviour.

Please note that infant assessments are not always predictive of later development.

We were very pleased to see NAME for this assessment. The next planned assessment through the Meconium Study will be at 4 years of age, pending funding.

Susan Fisher, M.A., C.C.R.C.
Psychology Assistant

Dianne E. Creighton, Ph. D., R. Psych.
Supervising Psychologist

cc: Dr. Ben Gibbard
Dr. Margaret Clarke
Parents

B.3. Maternal Willingness to Consent

B.3.1. Focus Group Interview Script

Welcome. Thank you for taking the time to come here today to share your thoughts with us about alcohol and drug testing of babies. Although there are ways to test mothers and babies for alcohol and drug exposure, there hasn't been very much research done about what women think about this sort of testing. We believe that it is really important that women's thoughts and views are heard.

During this focus group, I will be asking you several different questions about pregnancy and testing of babies. The interview will be tape recorded but only the researchers will be able to access the information. Your name will never be used. This makes sure that your name is never linked to anything that you say.

We ask that you remain respectful of each other throughout the focus group. Please allow women to finish their thoughts before speaking and let everyone have a chance to share their views. If you feel that you no longer want to be a part of the discussion, feel free to leave at any time. If anything we talk about today upsets you or affects you negatively, we have a trained and experienced counsellor here who you can talk to. We have food and refreshments here for you, so feel free to help yourself to them throughout the focus group. Comment on washrooms.

Introductory question: Tell us your name and an activity that you enjoy?
Perceived Threat/Perceived Susceptibility/Perceived Severity

- What are the greatest difficulties for pregnant women in this community?
- Who do you think is most likely to use drugs and/or alcohol during pregnancy?
- Do you think women are aware of any harmful effects of alcohol and drug use on the pregnancy?
- Do you think alcohol and drug testing mothers and babies is a good idea? Why? Under what circumstances?

Perceived Benefits/Perceived Barriers

- How would you decide which babies should be tested? Do you think there should be specific guidelines etc? What criteria should be used in deciding who should be tested?
- Do you think women should be able to decide whether or not their baby is tested? Under what conditions do you think she may not need to be asked?
- Why would a woman give consent for her baby to be tested for alcohol and drug exposure?
- Why would a woman not give consent for her baby to be tested for alcohol and drug exposure?
- What information should a woman have in deciding whether or not to consent to testing?
- Under what conditions should a doctor be permitted to test a baby without consent?
- What should happen if a baby tests positive for alcohol exposure?
- What should happen if a baby tests positive for drug exposure?
- What should the results of an alcohol screen be used for?
- What should the results of a drug screen be used for?
- How would you feel if your baby was tested without your knowledge? What if your baby was tested but your friend's baby was not? How would that make you feel?
- When you first saw the poster or when you decided to participate in this study was there any one thing that you really wanted to tell us?

B.3.2. Willingness to Consent Questionnaire

Note: Formatting of the Willingness to Consent Questionnaire has been modified to fit the formatting of this thesis.

Study ID: _____ Week Questionnaire Completed: Week of Monday. _____ _____ _____
Day
Month Year
Hospital: PLC FMC RGH Start time:_____ Finish time:_____

I am a research assistant working with researchers from the University of Calgary and the Calgary Health Region.

I would like to ask you some questions about your opinion of how and when drug and alcohol testing of newborns should occur. Your answers are confidential.

Tests to identify infants who were exposed to alcohol or drugs during pregnancy are being developed. Tests can be performed on an infant's urine, hair, and first bowel movement. These tests may help identify children at risk for problems like developmental delay and identify women and children who may benefit from extra medical help. I would like to emphasize that these tests are **NOT** in routine use in Canada right now.

In some countries this sort of testing is used in making decisions related to temporary care of children. Children may be temporarily placed in care while the mother is assessed. The policy in Canada is that mothers and babies stay together unless it unsafe for the baby.

One strategy of testing for alcohol and/or drug exposure of newborns is to test everyone. This is called Universal Testing. However, most universal programs, for example prenatal HIV screening, allow women to opt-out or refuse testing. I would like to stress that Universal Testing for drug and alcohol exposure is NOT **currently used in Canada.**

Before I continue, do you have any questions about what I just told you?

I'm going to present a scenario to you and then ask several questions related to the scenario.

Jane Doe is pregnant. Dr. Smith explains that drug and alcohol use during pregnancy can harm a baby.

Jane Doe's baby was exposed to alcohol and drugs during pregnancy and is at risk for 'developmental delay'. Please indicate your agreement with the following statements using 'Strongly Agree', 'Agree', 'Undecided, 'Disagree', or 'Strongly Disagree'.								
Dr. Smith should be able to test Jane's baby without asking for her consent if the consequence of a positive test may be that:	1	**Her baby will be temporarily placed into care while Jane is assessed for drug and alcohol problems and receives help.**	SA	A	U	D	SD	N/A
	2	**Jane and her baby will stay together and they both receive the help that they need.**	SA	A	U	D	SD	N/A
	3	**Jane and her baby stay together but neither receives any assessment or extra help.**	SA	A	U	D	SD	N/A
	4	**Jane and her baby will stay together while only Jane receives the help that she needs. Jane's baby receives no extra help.**	SA	A	U	D	SD	N/A

I will now ask you questions related to Jane's consent to testing in the same scenario.								
Jane should consent to the testing of her baby if the consequence	5	**Her baby will be temporarily placed into care while Jane is assessed for drug and alcohol problems and receives help.**	SA	A	U	D	SD	N/A

of positive test may be that:	6	**Jane and her baby will stay together while they both receive the help that they need.**	SA	A	U	D	SD	N/A
	7	**Jane and her baby stay together but neither receives any assessment or extra help.**	SA	A	U	D	SD	N/A
	8	**Jane and her baby will stay together while only Jane receives the help that she needs. Jane's baby receives no extra help.**	SA	A	U	D	SD	N/A

Jane Doe should receive information from her care-provider about drug and alcohol screening:							
9	At her first prenatal visit.	SA	A	U	D	SD	N/A
10	Additional information should be given after the birth of the baby and prior to the collection of the sample for testing.	SA	A	U	D	SD	N/A

Please indicate your agreement in each of the following questions using 'Strongly Agree', 'Agree', 'Undecided, 'Disagree', or 'Strongly Disagree'. If drug and alcohol testing was used, Jane would need to know							
11	How much drugs or alcohol makes a test positive.	SA	A	U	D	SD	N/A
12	What happens with a positive test result.	SA	A	U	D	SD	N/A
13	Who has access to the information.	SA	A	U	D	SD	N/A
14	How effective medical care is for children who test positive	SA	A	U	D	SD	N/A
15	The chance that a baby will have a problem if a test is positive.	SA	A	U	D	SD	N/A

Thank you. We are now done with the scenarios related to Jane Doe and her baby.

DRUG AND ALCOHOL SCREENING

I would like to ask you some general questions about drug and alcohol testing. **Please indicate your agreement in each of the following questions using 'Strongly Agree', 'Agree', 'Undecided, 'Disagree', or 'Strongly Disagree'.**

In your opinion, if all babies are routinely tested then the following may be the result:							
16	Women will cut back on drug and alcohol use during pregnancy if they know their baby will be tested at birth.	SA	A	U	D	SD	N/A
17	There will be a decrease in the number of children born exposed to drugs and alcohol.	SA	A	U	D	SD	N/A
18	If they are tested babies will get the help they need early in life.	SA	A	U	D	SD	N/A
19	If all women are tested no one will feel like they are being discriminated against.	SA	A	U	D	SD	N/A
20	Women will have babies at home to avoid drug and alcohol testing.	SA	A	U	D	SD	N/A
21	Women will be less likely to seek prenatal care.	SA	A	U	D	SD	N/A
22	Women will be less likely to trust their health care providers.	SA	A	U	D	SD	N/A
23	Anxiety about testing will actually increase drug and alcohol use.	SA	A	U	D	SD	N/A

24	**All women are aware of the potential problems for children who were exposed to alcohol during pregnancy.**	SA	A	U	D	SD	N/A

25	**Care-providers (e.g., doctors, nurses) can predict who used drugs or alcohol during pregnancy based on appearance, ethnicity, years of school, occupation, or socioeconomic status of a patient.**	SA	A	U	D	SD	N/A

UNIVERSAL TESTING
One strategy of testing for alcohol and/or drug exposure of newborns is to test everyone. This is called Universal Testing.

26	**You would support universal testing of babies for drug and alcohol exposure in which women are allowed to refuse testing of their infant.**	SA	A	U	D	SD	N/A
27	**You would support universal testing of all babies as part of routine care (i.e. women do not provide special consent).**	SA	A	U	D	SD	N/A
28	**If Universal testing for drug and alcohol exposure was performed in Alberta you would consent to the testing of your baby.**	SA	A	U	D	SD	N/A

PRENATAL CARE/ KNOWLEDGE & INFORMATION
The next couple of questions are related to prenatal care and information you received during pregnancy. Please answer 'yes', 'no', or 'don't know'

29	**Have you ever attended prenatal classes?**	Yes	No	DK	N/A
30	**Did you receive prenatal care during this pregnancy?**	Yes	No	DK	N/A
31	**Who provided the majority of your prenatal care?** ☐ Family Physician ☐ Low risk maternity Clinic ☐ Obstetrician ☐ Midwife ☐ Other_____				

32	**Do you feel that you had enough information about how to have a healthy pregnancy?**	Yes	No	DK	N/A
33	**Of the following, on which would you have liked to have received additional information? Check all that apply.**	☐ diet ☐ caffeine use ☐ smoking ☐ exercise ☐ alcohol ☐ stress		☐ pregnancy-related medical complications ☐ over the counter drugs ☐ none ☐ other_____	
34	**Did your care-provider ask you about alcohol or drug use during your prenatal visits?**	Yes	No	DK	N/A
35	**Of the following, what did your care-provider tell you about alcohol use during pregnancy? Check all that apply.**	☐ none is best ☐ try & cut down ☐ drink in moderation		☐ occasional drink is fine ☐ a drink per day is fine ☐ not discussed ☐ don't know	
36	**Of the following, what do you feel is an appropriate level of alcohol use during pregnancy?**	☐ none is best ☐ try & cut down ☐ drink in moderation		☐ occasional drink is fine ☐ a drink per day is fine ☐ don't know	
37	**Of the following, from whom did you receive information about alcohol use during pregnancy? Check all that apply.**	☐ doctor ☐ media (TV) ☐ friends ☐ family ☐ partner		☐ nurse/midwife ☐ books ☐ From Here Through Maternity booklet ☐ other	
38	**Did all of your sources of information tell you the same thing?**	Yes	No	DK	N/A

Support

I would now like to ask you some questions about the support you received during pregnancy. Please indicate your agreement using 'Strongly Agree', 'Agree', 'Undecided', 'Disagree', or 'Strongly Disagree'.

During pregnancy you feel you received support from:

39	**Health care providers (e.g. doctors, nurses, midwife)**	SA	A	U	D	SD	N/A
40	**Partner**	SA	A	U	D	SD	N/A
41	**Friends**	SA	A	U	D	SD	N/A
42	**Family**	SA	A	U	D	SD	N/A
43	**Best Beginnings**	SA	A	U	D	SD	N/A
44	**Your prenatal class**	SA	A	U	D	SD	N/A
45	**A Support group**	SA	A	U	D	SD	N/A

DEMOGRAPHICS

In conclusion, I would like to ask you some background questions. Your answers are confidential and will only be used to describe the participants in this study.

How old are you?

(1) 18-19 (2) 20-24 (3) 25-29 (4) 30-34 (5) 35-39 (6) 40+ (9)No answer

What is your current marital status?

(1) single (never married)	(3) common law/live with partner	(5) separated	(9) no answer
(2) married	(4) divorced	(6) widowed	

What is your occupation (e.g. lawyer, farmer, teacher)? _____ F/T or P/T

What is your partner's occupation (e.g. lawyer, farmer, teacher)? _____F/T or P/T

Not including your new baby, how many children have you had? _____

What is the highest level of education that you have attained (completed)?

(1) Elementary (Grades 1-6)
(2) Junior High (Grades 7-9)
(3) Some High School (Grades 10-11)
(4) Graduated High School
(5) Some Trade, Technical, Vocational School or Business/Community College (e.g. SAIT, Devry)
(6) Some University (e.g. University of Calgary)
(7) Completed Trade, Technical, Vocational School or Business/Community College (e.g. SAIT, Devry)
(8) Completed University Undergraduate Degree
(9) Completed Post-Graduate Degree or Professional School
(10) Other, specify: _____
(88) Don't know
(99) No answer

How would you <u>best</u> describe your ethnic origin (race)?

(1) African American/Black
(2) Caucasian/White (e.g. English, French, German, Irish, Polish, Scottish, Ukrainian)
(3) Chinese
(4) Filipino
(5) Greek
(6) Italian
(7) Japanese
(10) Native/Aboriginal Peoples of North America
(11) South Asian (eg East Indian, Pakistani, Punjabi, Sri Lankan)
(12) South East Asian (eg Cambodian, Indonesian, Laotian, Vietnamese)
(13) West Asian/ Arab (eg. Armenian, Egyptian, Iranian, Lebanese, Moroccan)
(14) Other, specify: _____

(8) Korean (88) Don't Know

(9) Latin American (e.g. Brazilian, Chilean, Mexican) (99) No Answer

LIFESTYLE

The following questions are related to lifestyle, for example smoking and alcohol use.

53. Did you smoke cigarettes before you became pregnant? Would you say that you smoked 10 or more cigarettes per day?	Yes ☐ <10 cigarettes per day ☐ ≥10 cigarettes per day	No
54. Did you smoke cigarettes during this pregnancy? Would you say that you smoked 10 or more cigarettes per day?	Yes ☐ <10 cigarettes per day ☐ ≥10 cigarettes per day	No
55. In the 12 months prior to pregnancy did you ever consume alcohol? For example, a beer, a glass of wine, a cooler, or a mixed drink.	Yes (administer T-ACE)	No (move to #63)
56. What type of alcohol did you usually drink? Please check all that apply.	Liquor Beer Mixed drinks/cocktails	Wine Coolers
57. How much did you drink in a typical week?	Amount:_____ drinks/week	
58. Did you ever drink 5 or more drinks on one occasion in the 12 months prior to your pregnancy?	Yes	No

We ask all women who have consumed alcohol the following questions… (source: T-ACE)		T-ACE SCORE (*not read to participants*)
59. How many drinks does it take to make you feel high?	_____ Drinks ☐ Don't Know ☐ No Answer	____ **2** - ≥ 3 drinks **0** - < 3 drinks
60. Have people annoyed you by criticizing your drinking?	Yes ☐ Don't Know No ☐ No Answer	____ **1** – Yes ____ **0** – No
61. Have you ever felt you ought to cut down on your drinking?	Yes ☐ Don't Know No ☐ No Answer	____ **1** – Yes ____ **0** – No
62. Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover?	Yes ☐ Don't Know No ☐ No Answer	____ **1** – Yes ____ **0** – No
		_____ TOTAL T-ACE SCORE

Note: If a subject cannot answer question **59** then code the total T-ACE score as **88**.

63.a. Did you drink any alcohol during this pregnancy?	Yes	No
63.b. Did you drink during this pregnancy but before you knew you were pregnant?	Yes	No
64. TRIMESTER	___ 1st ___ 2nd ___3rd	
65. Specify Type (check all that apply)	☐ **Liquor** ☐ **Beer** ☐ **Mixed drinks/cocktails**	☐ **Wine** ☐ **Coolers**
66. AMOUNT	**_____drinks/ week**	

I would now like to ask 4 more questions related to Jane's scenario.								
Jane should be able to refuse the testing of her baby if the consequence of a positive test may be that:	67	**Her baby will be temporarily placed into care while Jane is assessed for drug and alcohol problems and receives help.**	SA	A	U	D	SD	N/A
	68	**Jane and her baby will stay together while they both receive the help that they need.**	SA	A	U	D	SD	N/A
	69	**Jane and her baby stay together but neither receives any assessment or extra help.**	SA	A	U	D	SD	N/A
	70	**Jane and her baby will stay together while only Jane receives the help that she needs. Jane's baby receives no extra help.**	SA	A	U	D	SD	N/A

CONCLUSION

71. Before I go, is there anything you would like to tell me about a woman's role in deciding if her infant is subject to drug and alcohol testing?

_____
_____
_____
_____

Thank you for taking the time to complete this questionnaire. Do you have any questions?

72.

_____
_____
_____
____

I just want to remind you that our contact information is on the card that I gave you as well as on the consent form. Please contact us if you have any questions about the study. Thank you.

73. Start time:_____ 74. Finish time:_____ 75. Time to complete:_____

APPENDIX C: SUPPORTING DATA

C.1. Maternal Willingness to Consent: Themes Identified in Focus Groups and Categorized by the Components of the Health Belief Model

Perceived Susceptibility/Severity/Threat of Deficits

The women in the focus groups made comments that could be grouped into the following themes related to perception of susceptibility and severity of deficits regarding drug and alcohol use during pregnancy.

- All women are at risk but individual women feel invincible, lucky, or are in denial about the actual affects of substances on their own child;
- Drugs and alcohol do not discriminate. It is difficult to predict who may use drugs or alcohol during pregnancy and SES is not a predictor of susceptibility;
- Women tried to fit their experience into the context of other women- there is always somebody at greater risk;
- There are inconsistent messages from care providers, media, community (friends, family) regarding healthy behaviors and lifestyles. Women wanted consistent message: Do not drink during pregnancy;
- There seems to be a gap in perception of minimum dose and threat but all women knew that drugs and alcohol during pregnancy can harm your fetus; and
- Drugs and alcohol are not different. Alcohol is a drug, it is legal but should be not treated differently because they are both poisons to the baby.

Modifying Factors and Cues to Action

The participants in the focus groups identified the following modifying factors and cues to action related to drug and alcohol use during pregnancy.

- There is insufficient formal and informal support during pregnancy;
- Lack of continuity of care with a care-provider inhibits honest discussion about drug & alcohol use;
- Women want information and testing early. Start early so that women have a chance to change during pregnancy and not have their baby apprehended;
- Trust and relationships with health care providers were important;

- Testing was a missed opportunities for change if women are not ready to change. “Rock bottom” might be having a baby apprehended;
- Peer groups being aware of pregnancy can lead to pressure to not use drugs and alcohol. There may also be negative influence of peers/spouses when the peers/spouse is using; and
- Women wanted to know what constitutes a positive test & how much drug is required to test positive.

Perceived Benefit of Action

Perceived benefits of testing include decreased incidence of exposure with an accompanying decrease in costs associated with fetal alcohol spectrum disorders, best chance for baby, and an opportunity to change. Screening may give a mother an opportunity to change and motivation to stay clean throughout the course of the pregnancy. In addition, women felt that potential benefits of testing would include access to support, rehabilitation, and counselling; an opportunity for information sharing; and an opportunity to break the cycle of abuse.

Barriers to Screening

Perceived barriers to testing include fear of apprehension, and potential harm to mother and child. In addition, the women identified the following barriers to screening:

- The system would not be able to handle the number of positives that would result;
- The cost of testing may be too high;
- Woman may say ‘yes’ out of fear;
- A ‘no’ may be seen to be the same as a positive test. If they say ‘no’, they may be labeled as a woman who is using or who fears the consequences of using;
- Screening may lead to decreased trust between health care provider and the mother, could cause friction;
- Apprehending babies almost reinforces addictions or makes the addiction worse. If a woman knows that her baby will be taken away, she may drink or use more;
- “If you are going to get consent, do it like this focus group and get consent in a proper way”; and
- The fear of loosing a child may be so great that women may avoid the hospital and deliver a baby at home or elsewhere.