May 2011 Issue 5

The International Medical e-Network devoted to
Fetal Alcohol Spectrum Disorders

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INTRODUCTION

My fascination for fetal alcohol science is continually fed by new studies and the incredible FASD work done by the dedicated people in our field. We are indebted to the world renowned FASD medical experts who have contributed the original articles which open this issue: Dr Sterling Clarren (US/Canada), Drs Sandra and Joseph Jacobson (US) Mr Nathan Ory (Canada) and Dr Kari Slinning (Norway). We are also fortunate to have enlightening contributions about FASD and the Law from Mr David Boulding and former Judge Anthony Wartnik.

Those of us who work in the FASD field accept that alcohol harms the human fetus, based on the evidence of the thousands of studies over the past 40 years. Animal model studies have established the damaging effects of alcohol on the fetal brains of rhesus monkeys, mice, rats, lambs, swine pigs, guinea pigs, etc. The library of Fetal Alcohol studies is expanding, as the animal brains under the microscope are getting smaller. We include abstracts of new studies investigating intoxicated Zebra Fish and Fruit Flies. Will the sceptics finally believe alcohol-related brain damage is real and is serious?

What matters is that we verify and share FASD information to discourage pregnant women from consuming alcohol, as well as encouraging their families and communities to support them. We will also work to improve the lives of people living with FASD. New studies are now providing evidence for promising intervention.

For the first time in this issue, we have included two abstracts that are not specifically "Fetal Alcohol" studies, Sex-Specific Role for Adenylyl Cyclase Type 7 in Alcohol Dependence", King's College London, UK, (Society of Biological Psychiatry, April 2011). We thought it may be of interest because it implicates a gene that could be a component contributing to fetal alcohol damage. The second study “A transient placental source of serotonin for the fetal forebrain", (Nature 472, 347–350, 21 April 2011, doi:10.1038/nature09972) shows the direct role of the placenta in the developmental programming of the fetus.

You will also find a new section, FASD Books.

We think you will find this issue of the FETAL ALCOHOL FORUM particularly interesting.

Please let us have your feedback at nofas-uk@midlantic.co.uk. You can download all 5 issues of the FETAL ALCOHOL FORUM from our website: www.nofas-uk.org. To be added to the FETAL ALCOHOL FORUM Mailing list, please click here.

We now turn you over to our contributing authors, FASD pioneers who have changed and improved the FASD landscape.

Susan Fleisher
Publisher

Vandana Alimchandani
Editor/ Technical Support Supervisor

Elizabeth Mitchell
Associate Editor
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I. PREVENTING FETAL ALCOHOL SPECTRUM DISORDER: TIME FOR A COMPREHENSIVE APPROACH

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In 1975 I entered fellowship training in Dysmorphology and Neuroscience at the University of Washington in Seattle. My first year of fellowship was a basic research year in neuropathology and neuroembryology. During that year I had the opportunity to carefully study the two brains of infants who had died at the time of birth and who had both been recognized to have the recently described condition, fetal alcohol syndrome (FAS). Both had died because their brains could not sustain life. What I saw left no doubt as to why they had expired. (1)

The brain evolves throughout gestation in a highly organized sequence of cell multiplications and migrations. Neurons replicate, astroglial cells build a scaffold, neurons use the scaffold to migrate from the their origins in the germinal matrix near the center of the brain to their final destinations in nuclei or the cortex, axons and dendrites grow to connect cells to one another and finally, oligodendroglial cells are made and produce myelin that insulate the axons from each other. Alcohol appeared to interfere with every single step along the way. (2) The abnormal structure of those brains was astonishing in its wide-ranging damage.

We hoped that publication of the study of these brains would lead to more serious concern about FAS than the initial reports themselves. But the paper seemed to raise more curiosity than concern. How could it be that a drug that had been used for so long had not been considered as a cause for such startling abnormalities before?

The answer was that brains like this had been seen before, but like FAS itself the association with alcohol exposure as the likely cause had not been made. Further, although the picture of one of the brains has been published and republished as an example of alcohol’s potential harm to the unborn, it is not the typical example. (Illustration) We now realize that while these abnormalities can be caused by alcohol, these brains were almost uniquely severely effected. Alcohol does indeed interfere with these organizational pathways routinely during exposure in pregnancy but typically the damage is microscopic and microcellular. The resulting brain at birth is normal size and grossly of normal shape and form.

In live born children, these changes are only detected with the most sophisticated research imaging techniques and the results of these changes are detected through a broad battery of brain cognitive...
and performance evaluations. The majority of the patients do not even have IQ scores that place them in the category of mental deficiency, nor do they have a specific single kind of impairment like a social communication deficit or a motor planning problem. Because of the subtly of the structural brain changes and the wide variety of patterns of poor brain performance that result, it really is not a surprise that detection has been limited and the role of alcohol in causation has been somewhat slowly accepted. Nevertheless, those individuals who are affected struggle throughout their lives with adaptive problems stemming from these diffuse structural changes in the brain. Although they may not qualify for special help because they are not severely abnormal in any one specific area of brain function, the collective result of so many cognitive and performance problems means that they really are not functional in the day to day world. I have watched as schools, social welfare systems, and the justice system struggle to help this population that does not fit into the categories for special consideration that have been previously established. Although their lack of a category for care is hardly the fault of those with diffuse brain damage like those with FAS, they are the ones who suffer and we are the ones who pay the final bills for their failures to become working stable members of society. (3)

Environmental agents that cause birth defects do not always cause specific recognizable birth defect syndromes. Based on dose exposure frequencies, quantities and timings of exposures in pregnancy, one might expect a variety of different adverse outcomes – a cleft lip in one child, a heart defect in another for example. It is now clear that the full fetal alcohol syndrome occurs in a minority of alcohol exposed pregnancies but that the brain seems to be the most vulnerable organ from alcohol damage. This had lead to the use of the team fetal alcohol spectrum disorder (FASD) suggesting that like autism, there is wide variety in the expression of the physical changes and the brain changes after alcohol exposure in utero.

It should be a goal of society to maximize the abilities of its citizens. Brighter healthier citizens are far more likely to contribute to society and require less in return. This is the basis for public school systems, early developmental programs, nutrition programs for needy infants and so on. Protecting fetuses from harm is just another component of this goal. Alcohol conservatively effects one percent of the population of developed countries and the prevalence might be much higher. (4) There should be an organized approach to preventing such a significant public health problem both because it is just to protect innocent new life and because it would be a clear cost savings for society.

Prevention of brain damage from alcohol has not been made easier through the science that has tried to understand the mechanisms of the malformations. Alcohol is a common and legal substance and while it can lead to alcoholism and many health and social problems it can also be used in safe and even potentially healthful ways. Numerous studies in animal models demonstrate that the risk for damage from alcohol exposure is complex. The most dangerous time for brain damage is in the first few weeks of pregnancy – when women may not know they are pregnant.

Unfortunately suggesting a specific amount of alcohol as safe during pregnancy is difficult. After all it is not what the mother swallows but what the fetus absorbs that is important. Maternal blood alcohol levels are not easily translated from numbers of drinks per se. First, most people do not consume “standard drinks” unless they drink exclusively in bars or only drink their own bottles or canned beverages. Most of the time people pour approximate amounts of hard liquor or wine into glasses of various sizes and have only a vague sense of exact amount of ethanol consumed. Even if people do know the exact amount consumed, that is only a part of the equation.

The blood alcohol level will be higher is a small woman than in a larger one consuming the same amount, usually higher in thin women than in heavier ones. Absorptions of alcohol can vary depending on the period of consumption and whether or not it is consumed with food and what types of food. Blood levels also vary in different people depending on metabolism. Fetuses also seem to have differing abilities to resist alcohol. It is for these reasons that the public health advise in the United
States and Canada has largely rested on a statement similar to "No exposure to alcohol equals no risk of birth defects." It is the only absolutely true statement, but it is also not a realistic or fully helpful statement. On the other hand any simple statement that purports to assure all women that any drinking pattern is safe is also untrue. No dosing pattern or timed exposures can guarantee that a conceptus will be harmed, neither can any pattern be guaranteed to be absolutely harmless. Beyond the problems of knowledge translation from the scientific evidence to a public health statement, this whole issue diverts the public and professionals from the more important pathways to FASD prevention. (5)

The most dangerous dosing pattern is high binge exposures leading to blood levels of drunkenness, once or twice a week. Women who drink are a cross section of the entire population and only about half of conceptions are planned. Ironically as we have learned more about the higher risk patterns of drinking, young women in college and in the work force have increasingly learned to drink on weekends in this high dose binge pattern – the very most dangerous pattern in early gestation – often before pregnancy is recognized.

What is needed is serious studies in social marketing that attempts to provide women who are at low or moderate risk of having infants with FASD and who want to reduce their risk further with appropriate knowledge so that they can assess their "relative risk" for having a child with an FASD and take independent action. This approach requires the development of multiple messages, the testing of the messages with women in various situations – married/unmarried, working in companies where social drinking is expected, women in different ethnic groups or social classes. There needs to be consistent and effective information provided to professionals who may have a hand in counseling women about their pregnancies that again goes beyond a simple discussion of dose-response.

There are common problems that could be addressed. For example, "I am building my career in an organization and we all go out drinking together after work on Fridays. I am early in my pregnancy and do not want my colleagues to know about that yet but I also do not want to drink with them like I used to. What should I do?" or "My boy friend insists that we can only have a good time if we drink. I am pregnant, but he insists I drink and tells me it won't harm the baby. What should I do?" Campaigns also need to be developed with clear messaging for those who care about a potentially pregnant women – mothers, siblings, boy friends/husbands, close friends to help with these real life problems of balancing the safety of the unborn and the life that is being lead.

There is then another direction that FASD prevention must also go. In the 1980's we noticed that the children who were coming into our clinic for FAS diagnoses were largely in the care of foster mothers and adoptive families. Even when the children were with their birth families, their birth mothers were often not a primary care giver. Over a three-year period we had made diagnoses of FAS in 160 children but only 10 of them were in the immediate care of their birth mothers.

We proposed a study that would reach out and find these mothers and develop a profile of their lives. That work showed that the mothers were patients themselves. About half were likely to have alcohol related brain damage too. They had had lengthy life histories of abuse. They had significant psychiatric problems beyond substance abuse and post-traumatic stress. They reported that when they tried to get help with mental health issues they were directed to substance abuse programs first and when they went for substance abuse treatment they were redirected back to mental health. In general they received little help. Importantly, these women received the best care from society when they were pregnant. Most had had multiple alcohol- exposed pregnancies and had lost most of the infants to the care of others. It looked like alcohol was a self selected therapy and pregnancy was a self -elected intervention.(6,7) Recognition of this situation has lead to the development of highly effective programs working directly with these kinds of high-risk women. But such program development must be made more widely available and studied for clues making them even more effective and efficient.
Finally, FASD prevention needs to be imbedded into any and all programs that might serve women at high risk. Assessment for FASD and risk for FASD should be part of intake like assessment for pain, hypertension and other common issues. This should happen in arenas like programs for violence against women, homeless shelters, alcohol treatment, mental health programs, and many others. Screening positively for FASD at intake should then lead to assessment in these programs with then referral to the programs organized specifically for FASD intervention and prevention.

In order to bring all of this together, maintain it, assess the components and improve the outcomes, an agency of government must be appointed to be in charge and be funded to carry out the necessary work consistently over time. In these days of tight budgets and a movement away from development of a social cloth this work is no less emergent. We hope to bring this vision of prevention to Canada soon. (8) We hope that such work informs similar efforts in other countries.


II. BIOBEHAVIORAL MARKERS AND THRESHOLDS OF EFFECTS IN FETAL ALCOHOL SPECTRUM DISORDER

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Although the long-term adverse effects associated with fetal alcohol exposure are increasingly well known, many women continue to drink heavily during pregnancy in the U.S. and throughout the world. As many as 13% of infants born in the U.S. are exposed to varying levels of alcohol during pregnancy, with a higher percentage found among disadvantaged populations.1 A critical area of scientific and public health concern is the need to assess the health risks to the fetus associated with prenatal exposure to alcohol not only at heavy but also at low-to-moderate levels and to determine the lowest levels of exposure at which adverse effects can be detected. In addition, identification of alcohol-affected children continues to be difficult due to the lack of specificity in behavioral diagnostic criteria and limited understanding of the pathophysiology of the disorder.

Our research on fetal alcohol spectrum disorders (FASD) has focused on identification of the neurocognitive effects of prenatal alcohol exposure and the patterns and thresholds of exposure at which these features become apparent. Sandra Jacobson was trained in developmental and clinical psychology with a special interest in innovative infant and child neurobehavioral assessments; Joseph Jacobson, in developmental psychology with special expertise in statistics and research design. We were first introduced to the field of behavioral teratology in the early 1980s shortly after our arrival at Wayne State University in Detroit. Behavioral teratology studies the long-term effects of prenatal exposure to neurotoxic agents on cognitive and behavioral development in animals and humans, a field of study that has also come to be known as “fetal programming.”

Shortly after our arrival at Wayne State, we were invited to collaborate on a study to determine whether chronic low levels of exposure to polychlorinated biphenyls (PCBs), an environmental contaminant found in Lake Michigan fish, posed a health threat to children. We recommended initiating the study with newborns since infant behavior would be less affected by other potential socioenvironmental confounding influences and because prenatal exposure could be prospectively documented with greater precision, which seemed important since the fetal brain is most vulnerable to neurotoxic insult. We also recommended using new more sensitive narrow-band tests of infant cognitive function rather than more general assessments, such as the Bayley Scales of Infant Development, to detect subtle effects. Narrow band tests, such as the Fagan test of recognition memory,2 have the potential to provide more specific information regarding the etiology and underlying mechanisms involved in the teratogenesis of a neurotoxicant and can ultimately provide the basis for more effective approaches to intervention and treatment. Two important findings emerged from this research: (1) a dose-dependent effect of prenatal PCB exposure on infant recognition memory on the Fagan test,3 and (2) an association of relatively low levels of prenatal exposure to this contaminant with reduced IQ at 11 years of age.4

In 1985, we initiated a collaboration with Robert Sokol to conduct a large prospective longitudinal study to try to determine the lowest levels of prenatal alcohol exposure at which adverse effects become evident, using a sensitive neurobehavioral infant assessment battery, which included the Fagan test.5 We expected that various prenatal exposures including alcohol would be associated with similar poorer cognitive development on these infant assessments. We recruited a sample of 480 inner city, African American mothers, all who drank at moderate-to-heavy levels at time of conception (≥ 0.5 oz absolute alcohol—the equivalent of 1 standard drink—per day); and a 5% random sample of those who either abstained or drank at lower levels. A detailed timeline follow-back interview was
administered at each antenatal visit to assess both quantity and pattern of drinking.6  Contrary to our expectation, the Fagan recognition memory measure, which had been so sensitive to PCBs, was unrelated to prenatal alcohol exposure at the moderate-to-heavy levels in our Detroit cohort. Instead, prenatal alcohol was related to slower information processing speed on the Fagan and cross-modal transfer tests and to longer reaction times at 6 and 12 months.7,8  These findings are consistent with other studies that have identified fetal alcohol-related problems in processing speed in older children9-12 and indicate that this impairment is already apparent in infancy (see also Kable & Coles13). Prenatal exposure was also related to poorer symbolic play, an early precursor of language development.5  By contrast, prenatal cocaine exposure was associated with a different pattern of neurocognitive deficits on the Fagan test, faster processing speed with less accurate recognition memory.14  Thus, the findings from our Detroit longitudinal research demonstrated that different prenatal exposures are associated with different neurobehavioral endpoints that can already be detected in infancy.

A. Detroit

B. Cape Town

Fig. 1. Frequency of drinking days/week in (A) Detroit and (B) Cape Town.

In the Detroit study we also found clear evidence of deficits in infants whose mothers drank at least 1 standard drink/day during pregnancy on average.15,16  This threshold was similar to that found in the data published by Streissguth and colleagues in their somewhat more heavily exposed Seattle 500 cohort10 and by Day and colleagues in their low-moderately exposed Pittsburgh cohort.17-19  It is important to emphasize, however, that the women in our Detroit cohort (and in most other populations of women who drink during pregnancy studied to date) rarely drink every day but tend to concentrate their drinking on a few days/week. In our Detroit cohort, only 1 of 480 women actually drank every day; most women who drank weekly concentrated their drinking on 1-2 days during the weekend (Fig. 1A).20  Thus, a woman who drank 1 drink/day on average was actually drinking 3.5-7 drinks/occasion. We found a similar pattern of drinking among heavy drinkers in Cape Town, South Africa, where a large majority of the women also concentrate their drinking on 1-2 days/week (Fig. 1B).21  These findings are important because laboratory animal studies have shown that ingestion of a given dose of alcohol over a short period of time generates greater peak alcohol blood concentration and greater neuronal22 and behavioural impairment23 than when the same or even a higher dose is ingested gradually over several days. Thus, women who consider themselves "social drinkers" and might think they are drinking at safe levels if they average 1 drink/day may actually be placing their fetus at risk when they concentrate their drinking and drink 4 or more drinks per occasion, which is considered a "binge."

Two recent studies have reported findings suggesting that light maternal drinking during pregnancy may be beneficial for the fetus. Data from the Western Australian Pregnancy Cohort found that
children exposed at light and moderate levels received better parental ratings on the Child Behavior Check List than those born to mothers who abstained. A similar pattern was seen in an analysis of data from the British UK Millennium Cohort, which found fewer scores above the cut-offs for behavior problems in children born to light drinkers than to abstainers on the parent-reported Strengths and Difficulties Questionnaire. These findings are inconsistent with a substantial body of evidence from large sample, prospective longitudinal studies in Pittsburgh, Seattle, and Detroit that have documented a broad range of adverse effects on growth, cognition, and behavior in infants and children exposed at low-to-moderate levels. A major limitation of both studies was the use of abstainers as the sole reference control group rather than a control group comprised of both abstainers and light drinkers. Light and moderate drinkers are often economically more advantaged, better educated, and physically healthier than abstainers, characteristics that are associated with more optimal child cognitive and behavioral outcomes. Data presented in both the Australian and British studies show that the abstainers' income and educational levels were more similar to the heavy drinkers and markedly lower than the light-drinking mothers. Thus, the apparent benefits of low level drinking in these studies are likely an artifact of the generally higher socioeconomic status of the light drinking groups.

The threshold for adverse effects in FASD may actually be lower than 1 standard drink/day for many individuals since there is considerable intra-individual variability in vulnerability to teratogenic effects. We have identified three maternal moderator variables—maternal age, alcohol abuse history, and an ADH1B polymorphism—that markedly increase the child's vulnerability to FASD. Observations from case studies of multiparous heavy drinking mothers indicate that each successive child is almost always more severely impaired than the previous one, a pattern that has been shown in controlled animal experiments to be due to maternal aging rather than parity. Similarly, alcohol-related deficits in cognitive function and physical growth are often most severe and in many cases seen primarily in infants and children born to women 30 years of age or older, even after adjusting for age-related increases in the amount of alcohol consumed. Possible explanatory mechanisms for this increased vulnerability include age-related changes in maternal alcohol metabolism, body fat-to-water ratio, and placental permeability. These data indicate that a moderate- to heavy-drinking mother who has given birth to an unaffected child when she was younger needs to be warned that her risk of having an adversely affected child increases as she grows older. We have also found that among women who drink during pregnancy a history of alcohol abuse and/or dependence increases the incidence and severity of effects on IQ scores in FASD. Another important moderator of vulnerability relates to the ADH1B polymorphism, which plays an important role in the rate of alcohol metabolism. In our Detroit cohort, we found a consistent pattern of reduced vulnerability to alcohol-related cognitive deficits in children born to women with at least one copy of the ADH1B*3 allele, which is found in about 20% of the African American population and is associated with more rapid alcohol metabolism.

Thus, the threshold for sensitivity to prenatal alcohol exposure is likely to be lower in children who are genetically more vulnerable and/or are born to mothers from one or more of these more sensitive subgroups, and even light drinking during pregnancy could put the fetus at risk where the mother or infant is particularly vulnerable. Although there is no evidence that an occasional drink during pregnancy is consequential, abstaining from alcohol during pregnancy is still the best advice the obstetrician can offer.

In 1996, S. Jacobson participated in a National Institute on Alcohol Abuse and Alcoholism (NIAAA) site visit to Cape Town, South Africa, to investigate reports by Denis Viljoen, a geneticist at University of Cape Town (UCT), of an exceptionally high incidence of FAS in the Cape Coloured (mixed ancestry) community. This population, composed mainly of descendants of white European settlers, Malaysian slaves, Khoi-San aboriginals, and black African ancestors, has historically comprised the large majority of workers in the wine-producing region of the Western Cape. The high prevalence of FAS in this community is a consequence of very heavy maternal drinking during pregnancy that is...
due to poor psychosocial circumstances and the traditional dop system, in which farm laborers were paid, in part, with wine. Although the dop system has been outlawed since the 1920s, regular and heavy alcohol consumption persists in a high proportion of women during pregnancy in this community21,44 despite extensive efforts to intervene to reduce pregnancy drinking. This visit led to our collaboration with Christopher Molteno, a developmental pediatrician at UCT, on the first prospective longitudinal cohort study of FAS in which extensive alcohol drinking histories were collected during pregnancy.21,39 This study has enabled us to examine alcohol effects across the spectrum of prenatal alcohol exposure from low-moderate in Detroit to heavy exposure and FAS in Cape Town (e.g., Dodge et al.,45 O’Leary et al.46). In the Cape Town cohort, we found deficits in the same narrow-band infant outcomes seen in Detroit, corroborating the findings from our moderate-to-heavily exposed Detroit cohort.47 We also found that alcohol-exposed infants performed more poorly on an Infant Numerosity Test,48 an assessment that has shown that infants as young as 5 months of age look longer at small number displays that are incongruent with their expectations (Fig. 2).

By contrast to the nonexposed infants, the alcohol-exposed infants did not look longer at a display that differed from what was expected. In the Cape Town cohort we have also found that performance on the Infant Numerosity Test is predictive of poorer arithmetic performance in childhood.49

In 2005, we received a Fogarty International Research Collaboration Award with Ernesta Meintjes, a UCT physicist, to initiate the first functional magnetic resonance imaging (fMRI) studies in Cape Town. The pilot study that our research team conducted helped lay the groundwork for the acquisition of a research-dedicated Siemens 3T Allegra scanner by UCT and University of Stellenbosch and the establishment of the Cape Universities Brain Imaging Centre, which has now enabled other FASD and pediatric researchers in Cape Town to use fMRI in their studies. Neuroimaging represents the new frontier in research on cognitive and behavioral impairment in FASD, making it possible to move beyond standard neuropsychological tests to examine the neural bases of the cognitive deficits found in these disorders.50-59 Because most neuropsychological tests are complex and multifaceted, they cannot provide information about the specific aspects of central nervous system function that may be affected. For example, children with FASD and ADHD often present with similar attention and behavioral problems that may or may not have a common neurophysiological basis.60-64 Castellanos and Tannock have advocated going beyond descriptive symptom-based approaches to diagnosis to identify specific biomarkers derived from cognitive neuroscience that are “closer to the site of the primary causal agent” than to the manifest behavioral phenotype.65 Following this model, we have been attempting to identify “biobehavioral markers,” behavioral endpoints that are altered by fetal alcohol exposure whose neural pathways or processes are relatively well understood.49

Our recent work has focused on two biobehavioral markers: eyeblink classical conditioning and

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magnitude comparison. Eyeblink conditioning (EBC) appears particularly promising because a deficit in this elemental form of learning is seen in a large proportion of alcohol-exposed children. In our Cape Town study of EBC at 5 years of age, conducted in collaboration with Mark Stanton, an expert on EBC, not a single child with FAS met criterion for conditioning as contrasted with 75.0% of the controls; two-thirds of the other alcohol-exposed children also did not meet criterion for conditioning, a pattern of effects that was also evident at school age (Fig. 3).

These findings are consistent with animal studies, which have shown that heavy exposure to ethanol during early development disrupts EBC in rat weanlings and adults. These findings are consistent with animal studies, which have shown that heavy exposure to ethanol during early development disrupts EBC in rat weanlings and adults.68-70 Because the neural substrates of EBC have been exceptionally well documented in laboratory animals, research on this endpoint provides an excellent opportunity to investigate neural processes that mediate the adverse effects of fetal alcohol exposure. Arithmetic is a domain of higher order cognitive function that is among the most sensitive to alcohol exposure in utero.18, 71-74 Moreover, alcohol-related deficits in exact calculation appear to be mediated by a specific deficit in magnitude comparison, the fundamental ability to represent and manipulate quantity.64 fMRI studies have identified a fronto-parietal circuit that mediates magnitude comparison,75 providing the basis for investigating the neuropathology that mediates this alcohol-related deficit in number processing.59 It is significant that the alcohol-related deficits in both EBC and arithmetic persist after control for IQ.18,21,64,67,76 Given that these deficits are specific features of FASD over and above the diminished overall intellectual ability associated with these disorders, a focus on these endpoints should be helpful in advancing understanding of the etiology of FASD and developing strategies for intervention and treatment.

Because both EBC and numerosity, a developmental precursor of magnitude comparison, can be assessed in infancy,48,77 these biobehavioral markers can also be used to evaluate the efficacy of novel prenatal interventions (e.g., supplementation with micronutrients) several months or years before standard neuropsychological assessments can be administered and to validate new diagnostic procedures (e.g., facial measurements from 3-D images78). They can also provide baseline data for evaluating novel postpartum interventions (e.g., therapeutic motor training79,80), whose efficacy for reversing or mitigating alcohol effects can be assessed by measurement again at the conclusion of the intervention. Future studies of fetal alcohol effects on specific components of the neural circuitry of both these biobehavioral markers have considerable potential for providing important new information regarding the pathophysiology of FASD, which can, in turn, contribute to the development of interventions and treatments that are targeted to the specific deficits that characterize this disorder.

References


Fig. 3. Examiner prepares child for eyeblink conditioning assessment.


in children with fetal alcohol spectrum disorder or attention-deficit-hyperactivity disorder. Dev Med Child Neurol 52:205-211.


III. HOW TO SORT OUT DEVELOPMENTAL BRAIN DYSFUNCTION IN FASD FROM EVERYTHING ELSE

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I am a behavioural psychologist and clinician with 35 years experience working with persons with intellectual disabilities, mental illness and extremely challenging behaviour. Susan Fleisher attended a presentation I gave in Vancouver in April 2010 titled, How to sort out developmental brain dysfunction in FASD from everything else. Following this she invited me to write an original article for the Fetal Alcohol Forum.

I work exclusively with complex cases that have come to my attention following the failure of other specialists to bring about lasting changes in behaviour. The effort to develop new patterns of more adaptive behaviour involves many levels of accommodation and usually, lengthy periods of training of support persons as well as of the child, youth or adult, with a lot of trial and error on both sides of this equation. Behavioural training of new skills also makes multiple assumptions about the presence in the individual of "intact" learning processes.

The approach I use is to not focus so much on the undesired behaviours that have led to the referral. Instead, I carry out extensive, functional behavioural analysis to look for windows of opportunity that can lead to alteration of disruptive or maladaptive behaviour patterns.

By the time an individual has been referred for behavioural or mental health issues it is likely that there is already a long history of approaches having been attempted with varying degrees of effectiveness. These individuals are usually inconsistent in their responsiveness, and present with a confusing diagnostic history. It is most likely in the case of persons with intellectual or other developmental disabilities that their learning processes are not entirely "intact".

In the field of fetal alcohol spectrum disorder (FASD), Diane Malbin suggests that when there is a clear diagnosis of brain dysfunction, rather than trying harder, it makes more sense to try things differently. Appropriate intervention goals in the FASD world are to try to create a "better fit" between the affected person as they are, and the world that expects them to be functioning according to more
familiar norms.

I have found the same approach applies to other brain dysfunctions occurring in the developmental period; autism, intellectual disability, Tourette’s, genetic syndromes affecting brain development or processes, etc.

I have found that focusing on the person and who it appears that they are “trying to be in the world,” can sometimes reveal strategies and approaches that have high likelihood of immediate positive response. This in turn sets up a mutually reinforcing cycle of interaction between support persons and the child or youth. I look for the individual’s comments and positive behavioural efforts that have stood out enough to be recorded in the various reports on file, or remarked upon by their counsellors and support persons.

The “outcome objectives” I am trying to achieve in these functional behaviour analyses are:

1. Reveal examples of how the individual thinks of him/her self and the type of effect this person is trying to have on their world. What interventions can be used to assist the person to have successful impact on their world as they live in it? Anywhere we can provide structured opportunities for personally effective feedback we are ensuring conditions where the individual will be paying attention at their level of ability!

2. Identify approaches that have already been shown to sustain positive relationships with the individual. Emphasize what already works and expand upon this. If we can show the individual and their support network how and where to do this, these approaches will be familiar so support persons won’t actually need to learn new skills. They will just need to “do some more” of what already works.

3. Look at the developmental trends in assessment history. Notice when areas of relative weakness appear to have reached a plateau. The “emotional” functioning level of the individual will often be a reflection of the age at which their developmental progress reached this plateau!

4. Clarify realistic expectations based on assessed and inferred discrepancies in intellectual and adaptive functioning. Approach the individual in areas of identified relative strengths with higher expectations. In areas of identified weaknesses; lower expectations, accommodate and be prepared to protect the person from their anticipation of failure and high arousal. The “developmental” functioning level of the individual will often be fixed by their areas of relative weakness.

Remember, it is always “everything,” not just one thing. To capitalize on “windows of opportunity” for successful intervention:

i) Provide emotional support to the individual at their estimated level of emotional maturity.

ii) Modify approaches according to individual’s assessed cognitive-developmental level.

iii) Adjust further according to areas of specific learning weakness.

iv) Accommodate to developmental brain dysfunctions that have been persistent and not likely to change in response to training efforts. These areas will not simply display “immaturity” but also severe qualitative differences from what would normally be expected at the implied developmental level of assessed skill. (This is what is often missed by those who are not familiar working with developmental brain dysfunction. It is not just “younger” functioning in these areas. It is qualitatively impaired functioning even at the “younger” level.)
v) Design explicit behavioural supports to offer enhanced positive feedback for existing skills, and provide environments where these can be elicited.

vi) Protect individual from identified historical triggers to mental health crises.

5) Look for opportunities to build habits for “peaceful co-existence” and coached, calming procedures that can be frequently rehearsed outside of periods of crisis and high-arousal. Find or create relevant metaphors that the individual can relate to as a “slogan” for self-control.

6) Identify and create non-chaotic responses for support persons to take to the individual’s most chaotic and least predictable behaviours. There need to be clear strategies in place to allow all the players to “survive” the chaos of crisis situations and predictable methods for re-engaging with the person following crisis that will sustain the ongoing, positive relationship with the individual.

How long does it take to undertake functional behavioural analysis to reach conclusions that will support an individual at this depth? In my work, reviewing historical files and conducting direct interviews requires somewhere between 10 to 30 hours of concentrated work. Committing this amount of time is reserved for only the most complex cases, but these are the very cases that require this level of attention to their complex profiles. It really is always “everything” and not just one thing.

A famous quote of Einstein’s is paraphrased as “Make things as simple as possible, but not simpler”. The actual quote was “It can scarcely be denied that the supreme goal of all theory is to make the irreducible basic elements as simple and as few as possible without having to surrender the adequate representation of a single datum of experience.” It also helps to have an obsessive personality and an extreme interest in detail.

I have converted my own obsessive interest in detail into a number of articles that you may find useful. These are posted on the website: http://fasdconnections.ca/id22.htm

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IV. FASD: A REPORT FROM NORWAY

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Up-to-date knowledge about how alcohol affects the brain of a developing fetus and the lifelong consequences of prenatal alcohol exposure is generally low among health professionals in Norway. A very low proportion of affected individuals are identified and diagnosed with FASD. Data from the Medical Birth Registry of Norway illustrates this situation; only 17 newborns were diagnosed with FAS from 1987-2005 (among 60,000 births per year). When children are referred to specialists, the evaluations are often too narrow given the broad spectrum of developmental areas that are affected in these individuals. The majority of children diagnosed with FASD live with foster or adoptive parents, and most of them have reached school age by the time they are diagnosed. The health authorities in Norway are aware of this situation and have taken several important steps in the last 6-7 years to improve it. In 2004 a group of experts in this field were invited by the Norwegian Directorate of Health
to write a report about alcohol use during pregnancy and the risk of FASD. Published in 2005, this report led to a national campaign advising pregnant women to abstain from alcohol use throughout their pregnancies.

Since 2006 the Borgestad Clinic, a treatment and competency center for drug abuse and addiction, and the National Network for the Study of Infant Mental Health have worked together to promote early intervention by increasing knowledge about children with prenatal drug exposure. The centres receive their basic funding from the Norwegian Directorate of Health, and their tasks are primarily defined by this directorate. The Borgestad clinic has a special in-patient unit for pregnant women and their partners which offers the opportunity to continue the treatment after delivery in a family unit where the family can live for several months.

The National Network for Infant Mental Health is a department in the Center for child and adolescent mental health (RBUP) established by the Ministry of Health and Care Services. The centres' primary tasks are research and postgraduate training and there are four centres placed in the main health regions. As a national network the main goals are research and to improve services relevant for infants, small children and their families, and more generally to contribute to the acquisition of knowledge about infant mental health.

Every year the Borgestad Clinic organizes a large national or Nordic conference about children affected by drugs pre and postnatally (3,500 participants, professionals only). In addition, it has been several one-day seminars for foster and adoptive parents in every region of Norway (100-150 participants in each seminar). In May 2007 our two competence centers jointly arranged a 3-day seminar on FASD for professionals from municipal and special health services with Diane Malbin from Oregon, USA. The purpose of the seminar was to provide a thorough introduction to the effects of prenatal alcohol exposure and the ways it affects the child as well as the family. In November 2008 we held a 2-day workshop for key professionals from the Nordic countries, both clinicians and researchers, in this field. The goal was to discuss a multi-methodological approach to assessment and diagnosis of children and youth prenatally exposed to alcohol and other drugs.

The Norwegian Directorate of Health has given our two competence centers additional economic support to develop and implement a training program in each of the five health regions in Norway. The overarching goal is to ensure that all residents of Norway, regardless of where they live in the country, will receive equal service options for assessment, evaluation and support/treatment when they suffer from the effects of prenatal drug exposure. The training takes place in two parts- Part 1 consists of a 3-day seminar on the effects of prenatal drug-exposure, assessing and diagnosing individuals from infancy to adulthood. Part 2 focuses on intervention in a family and system perspective. Part 1 in the training program has so far been carried out in the South Region, and next training will take place in May in another region. A third competence centre is involved in developing Part 2 of the training program; Sørlandet kompetansesenter. This centre has a special focus on intervention for children with special needs. Together we hope to make a Norwegian film about FASD to be used in secondary school and high school (age 13-18).

In addition to the training program we are developing, the Directorate of Health has started a project in certain municipalities in Norway to evaluate the use of screening tools for alcohol abuse, such as TWEAK and AUDIT, at the first checkup for pregnant women. The goals of our cooperative work on many levels in Norway is to prevent injuries from alcohol in newborn children, to identify a higher proportion of affected children and youth early on, and to offer help and support that is effective for the affected person and his/her family. As we are writing this report the Directorate of Health is finishing a new national guideline for pregnant women and families in methadone maintenance treatment. It is recommended that families with children up to 6 years are followed closely within a medical and psychosocial perspective with the purpose to support a positive development and mental wellbeing in each child and their parents. It is stated that this guideline includes all families that have children who
are affected by any type of prenatal drug exposure. The next step is to make sure that these promising words will be translated into action. We will work with this goal in mind!

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V. CALLING RESEARCH BRAINIANCS

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On behalf of legal professionals, I am asking the brain research community for help. Fetal Alcohol is a physical disability like blindness or quadriplegia. Fetal Alcohol, combined with other brain injuries, is the single biggest, most perplexing and difficult problem facing the criminal law today.

Justice system professionals need help because Fetal Alcohol and the attendant legal issues cannot be solved without the intellectual resources of brain scientists. I have tried to persuade judges, lawyers, police, probation, corrections, policy makers, and others that we need to do something different. Our method of jailing folks and then jailing them for longer and longer periods because they fail to grow new brain cells and develop new brain abilities while in jail the first time, is not working.

Lawyers desperately need research they can provide to a trial court judge, and research that makes sense to probation officers, prison administrators, and policy makers who advise the politicians what to do when amendments to the criminal code are discussed. This daunting task requires brain research to back up what most criminal lawyers know from daily experience.

The system is failing because the criminal law system is built on two assumptions that are not valid for persons with Fetal Alcohol or with other brain-based difficulties. First, the criminal law assumes all citizens can learn from our mistakes. Second, the system assumes those arrested and convicted and other nascent criminals who hear about the convictions can learn from the mistakes of others. These principles are called specific and general deterrence. These technical terms, if they have any validity, are only valid when you have a brain comparable to the brain of an appellate judge. I have never met a criminal who said, “Just before I smashed his head to the wall, I considered what the newspaper and other media said last week about the Court of Appeal’s game changing ruling in R. v. Concrete.”

The modern criminal law system was largely formed in the 1800’s, when knowledge about brains was concerned about counting bumps on the skull. The signal feature of criminal law in all democracies, again from the 1850’s, is the set of rules developed about insanity. Known as the McNaughten Rules, these rules speak to mental states and what defences are available. They were made law some 16 years before Sigmund Freud was born. The Rules written by the House of Lords, in effect, say: “If you knew it was wrong, you are not insane and we can hang you.”
Daniel McNaughten was a paranoid schizophrenic and an angry Scotsman who desired a Scotland free from domineering English rule. He aimed to shoot the English Prime Minister and missed, killing his secretary instead. He was acquitted by a jury based on a defence that he was insane. The House of Lords, Queen Victoria, and much of the English elite society were not amused. The House of Lords essentially held another trial for themselves without Daniel. After listening to the experts and reviewing the transcript, they formulated a series of rules to bring clarity to the law, or as some believe, to make sure this miscarriage of justice never happened again.

The problem is not that the House of Lords made mistakes: it is that the courts have not kept up with brain research and the system is mired in thinking that was current a generation before Freud was born. The House of Lords had no access to modern thinking, let alone Magnetic Resonancing Imaging (MRI) technology and other modern tools we regularly use to see the brain.

Thus, the legal system has a tendency toward failure for brain-injured persons because modern science is not a part of the legal process. Modern brain research has not permeated deep enough to change the fundamental Victorian mindset that underpins legal thinking all over the world. We have been tinkering at the edges and refuse to consider that the whole enterprise may be fundamentally flawed at the core. We quickly resort to wholesale accusations of “bad character” or “bad upbringing” or “bad environment” or the latest, “bad genes” rather than consider the individual’s brain relying on the modern research.

I am confident that if policy makers, judges, lawyers, police, probation, and prison officials knew what the brain research community knows today, the laws would be different. I believe that only brain researchers can provide the needed information required to update the McNaughten Rules.

The McNaughten Rules are only one aspect that begs for change. Our practices on sentencing, our notions of guilt and degrees of guilt, and foremost, the threshold to charge a criminal offence, will someday soon all change when brain research is brought, probably screaming and kicking, into Parliament and into the courtroom.

Research that connects the advances in brain science to the problems seen in trial courts is available. Judges and lawyers do not have time to read NATURE, THE JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM, OR MOLECULAR PSYCHIATRY in addition to their heavy case loads. Judges and lawyers must read thousands of pages of materials weekly merely to keep up with the advances in law. At continuing legal education seminars, lawyers are always interested in the advances in brain science. These seminars tend to be aimed at the lawyers who do car accident and medical malpractice law. Sadly, family and criminal lawyers are the ones who should be considering brain science most often. Most child custody cases have issues involving brains. It may be that the parents have a mental health issue or a cognitive disability. The judge must decide which one has the more competent brain with which to raise the children.

We know more about brains than we did when I was in law school in 1984. And I am learning now that we in the legal field really know very little about brains. Judges are faced with a complex problem. Judges rely on experts chosen by the lawyers. The lawyers choose experts the lawyers believe will win cases. Here self promotion, publicity and notoriety seem to overrule science. And then the beleaguered judge must decide. Often what happens is that the Judge falls back on “common sense.” This is likely to be disastrous if the common sense comes from television or from conversations over coffee with other judges.

We are all aware of judgment after judgment where basic brain science is ignored.

In a famous murder case, a prosecutor said on Canadian national television that “the accused has two different diagnoses of Fetal Alcohol: one when he was 12 and a second one when he 15 years old. The prosecution believes the accused (now convicted of first degree murder) has outgrown these
diagnoses now that he is an adult at 22 years old."

Brain research does not support the notion that he grew new brain cells after his 18th birthday.

A second case was a sex assault guilty plea. Hint: Fetal Alcohol clients almost always have guilty pleas. The good judge writes: "I find that the accused had Fetal Alcohol at the time of the offense". He was a good judge because he considered the expert report, which said, among other things, that the accused had the developmental skills of someone of about 12 years old. Sadly, the judge continued saying "and I find that his Fetal Alcohol did not impair his judgment to the extent he was unable to appreciate the wrongfulness of his behaviour."

The judge in the second case knew little about brain science. And it is not his fault. The lawyers should have told him and sadly they did not because they too knew little about the brain science. The lawyer for the defence was probably so excited to get a good judge and a good deal on sentence that he was reluctant to point out the fatal mistake in the otherwise positive judgment.

To solve this problem of inadequate brain science knowledge, I need Harry Potter's magic wand. Equipped with a magic wand, I would like to stop time and bring the people of the legal system (all of them) into a locked arena bigger than the Coliseum and begin a teaching session on basic brain science.

I would rely on Dr. Kathy Sulik from the University of North Carolina, Dr. Brian Christie from the University of Victoria British Columbia (B.C.), Dr. Sterling Clarren, formerly from Seattle and now in Vancouver, B.C., Dr. Ed Riley from San Diego State University, and Dr. Catherine Gould from Princeton. I would also require essay questions compelling these legal professionals to read Carl Sagan, Loren Eisley, Lewis Thompson and T.S Kuhn. This fantasy is probably impossible.

So, your help is necessary. Brain researchers are required who can write about brains the way Carl Sagan wrote about the Cosmos. If brain researchers would read the criminal cases from Australia to Alaska and from Alberta to East Anglia, you would call up the criminal lawyers involved and say, "You need to read my paper".

Lawyers need brain research to be digestible, so when a police constable in Tasmania or Texas reads it, he knows the guilt of the person he has arrested is not the issue. The issue is always: what do we do now.

I know that researchers want this brain information out there where it can be used for the public good. When I have telephoned experts like David Nutt, Brian Christie, Ed Riley and Kathy Sulik, all of them have answered with emails and phone calls, and when cornered at a conference, all have been extra generous with their time and expertise. One expert lamented. He wished he had a person on staff he could talk to, and then the person would go away and write up his research for him so that could be published in a popular magazine.

I would like NOFAS to set up a brain research listserv for the legal system, a computer-driven chat room specific for purpose of sending useful brain research to the legal system. I would like members of the brain research community to call some folks I know who would spread the information to where it would do the most good:

Tom Smith is a retired judge who writes to educate other judges.

Diane Malbin is the author of the best book on Fetal Alcohol Spectrum Disorder ("FASD") entitled: TRYING DIFFERENTLY, NOT HARDER. She is the innovator of the Neuro-Behavioural model.
Susan Brooks is an Associate Dean for Experiential Learning at Drexel University's law school in Philadelphia. She teaches law students.

Jan Lutke as the world's premier FASD advocate and the force behind the Vancouver FASD conference. She can inform the world.

Kristal Bodaly is a speech and language pathologist at the Asante Centre in Maple Ridge, B.C. She is writing 900-plus page interactive text on FASD and the legal system. It will soon be available for free on the internet for parents and legal professionals.

Rod Snow is the President of the Canadian Bar Association and is the force behind Canada's Fetal Alcohol Resolution (Niagara Falls 2009).

These are the people who will drive the movement to repair the McNaughten Rules. They will develop new programmes, and they will bring some humanity to criminal law if they have the brain research they need at their fingertips. Many others would also gladly join a properly moderated listserv dedicated to explaining brain science to lawyers and judges. (An example of a successful multidisciplinary listserv is the one run by Professor Daniel Lietchty of University of Illinois, which is dedicated to the work of Ernest Becker.)

The brain research community also needs to find the grant money to start several blogs. Perhaps one could be named: CALLING THE NEXT WITNESS: BRAIN SCIENCE GIVES EVIDENCE IN COURT. Unless this new brain science information is shared with lawyers, we will continue to put many, many, many, people in jail and then when they re-offend, we will put them away for longer and longer prison times.

The standard objections I have heard to stopping this viral jailing of persons with Fetal Alcohol are: 1) Prisons may cost a lot but they save money in the end; 2) We are not wasting money because there are good union jobs in jails; 3) Jails are necessary because there is no other way to protect the public; 4) And the big one--this is not the right time politically to update the McNaughten Rules.

Brain science is desperately required to reform the legal system. If the facts are agreed upon, criminal law can usually be reduced to one question. For 99.9% of Fetal Alcohol clients, the facts are never in dispute. The question is: what were you thinking? Here is the surprise. Often the person was not thinking. Or at least they were not thinking like you and I think. People with brain insults, whether occurring in the womb or from a motorcycle accident, are not thinking like the clear-minded jurists who wrote the McNaughten Rules.

Criminal law, especially from the Legislature and Courts of Appeal, is written by and for people with complete brains. Good science always drives good social policy, and good social policy always produces good judgments. Lawyers need research that will help people with Fetal Alcohol to become taxpayers. Lawyers need research on what brain-based interventions work, and they need research on brains that show the reasons a particular intervention works and why. What does a successful intervention look like?

My assumption is this world needs all the help we can get and that putting people in jail a second, third, and fourth time is not helpful.

Her are two examples of what is needed.

I asked Dr. Christie what I could say to the legal system professionals in Iqaluit, Nunavut. He is doing brain research on mice. He has four groups of mice: (1) mice with Fetal Alcohol; (2) mice without; (3) mice with Fetal Alcohol with access to a treadmill; and (4) mice with Fetal Alcohol without access to a...
treadmill.

He says his research shows that the treadmill exercise helps brains repair some of the damage done by alcohol in the womb. This idea of the value of exercise is the subject of Dr. John Ratey's book entitled SPARK. Dr. Christie said to me: "20 minutes of exercise in the morning, do not make them sweat, do not make it competitive, and repeat after lunch". In SPARK, Dr. Ratey details the success of this physical exertion in many schools.

While Dr. Christie's quip has the ring of simplicity, to probation officers, corrections staff, and judges it also has the ring of hope and gives meaning to some of the solutions they can try to create. This advice works on so many levels.

Another example of research lawyers can use in the courtroom is the mice brain photographs of Dr. Sulik and her team of embryologists. These pictures can be shown to members of the legal system because they are available for free online and they show the damage alcohol in the womb does to brains. The pictures diminish the value of any debate over the accused's inherent bad character, bad upbringing, bad genes, or bad environment, and show the way to creating solutions.

It is a start. And it is not enough.

Judges need more brain pictures. They need intervention studies on brain-based techniques that work for certain ages, and for certain brain functions and dysfunctions. Probation officers and prison guards need research on diet. Lawyers need research to show conclusively that all behaviour is brain-based, and that by seeing how the brain works the legal system can help people. The system needs studies that show which part of the brain houses impulse-control, suggestibility functions, prediction, and abstracting skills. Lawyers need photographs a jury can see that will prove that the prisoner's brain is missing these parts.

We need more scientists like Dr. Fred Bookstein. He goes into the courtroom and tells the judge and jury: "If this part of the brain is damaged, the two central assumptions of the legal system that we can learn from our mistakes and that we can learn from the mistakes of others may not apply to the person in the prisoner's box." He is a statistical brain morphologist and explains what "normal" brains look like on MRI pictures. He puts up the prisoner's pictures and his own and explains the differences. Judges and juries always appreciate good information.

Someone needs to create a science of the whole person, a science of relationship. The roles of the cascades of chemicals in the brain when we love, smile, kill, hurt, or fail to act need to be explained like Newton's Laws were explained in high school.

Lawyers need scientists to design brain-based accommodations, so the good people in the prisons and the fine probation officers I have met can learn to access the person with Fetal Alcohol via their limbic system, and can develop meaningful relationships with their clients. Almost as if by inertia, prisons and probation services tend to rely on old behaviourist (punish or reward) style interventions. These methods fail those with compromised brains.

We need scientists to stand up and see their work as a part of the larger world, and those same scientists need to develop public speaking skills and go on YOU TUBE, FACEBOOK, TWITTER, and listservs dedicated to educating legal system and the public about brain science.

I have found out that once people realize that the person with Fetal Alcohol has a brain that is missing pieces, everything changes. If they choose to develop a relationship in the sense of the renowned psychologist Dr. Carl Rogers, then we can create the "external brain"—a caring committee of individuals—as developed by Dr. Sterling Clarren. And then everything gets better. These methods
lead to positive outcomes, and jail is not always required. Without brain research these methods will remain esoteric, untested, and "on the fringe."

A word here about the obvious. I am not trying to keep all people out of jail all of the time. In many cases jail is a good place and does make society safer for a short time. The incarcerated are warm, fed, and can sleep safely. The structured routine of jail can assist later release plans.

Jail is a brutish place where many ugly rapes occur. I know. I object to the expensive warehousing of people with imperfect brains when other positive alternatives exist.

Jail is the default solution. When schools, social services, families, communities, and other safety net services fail, people with brain-based birth defects end up in jail because we do not have the science to convince governments to build more appropriate resources.

These cheaper resources include halfway houses with supervisors skilled in brain science, brain-based supervision in the community, and supervised "practice" jobs that lead to real jobs. They also include programmes that develop our shared humanity by stressing research-based ideas that work, not programmes that warehouse those with brain-based birth defects.

You have the science; share it please.

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### VI. A JUDGE’S PERSONAL FASD JOURNEY IN PURSUIT OF JUSTICE

**Anthony P. Wartnik, Judge (Retired)**  
Mercer Island, WA., USA  98040

I had practiced law from 1963 until January of 1971 when I took office following a successful election to the Bellevue District Court. As a child growing up in Los Angeles, California, I had consciously experienced the impact of having an alcoholic father and the consequences of his illness starting at about 12 years of age. I believe that this experience influenced the fact that I took a special interest, as a lawyer and a judge, in clients and litigants who became involved in problems with the juvenile and adult criminal courts and in family law or marital dissolution cases as a result of alcohol abuse.

As a young judge in our limited jurisdiction judicial system, I was dealing daily with assaults resulting from intoxication and driving under the influence of alcohol cases and earned a reputation as someone who was knowledgeable about and sensitive to the substance abuse issues that came before me in court. I was even nominated by our local alcohol information and referral service agency for my work on the bench for, and was ultimately recognized by the Washington State Junior Chamber of Commerce as one of three Outstanding Young Men in the State of Washington. I mention this because it wasn’t until almost twenty years following that recognition when, as a King County Superior Court Judge, sitting at our Juvenile Court Division, that I was first introduced to the subject of Fetal Alcohol Syndrome (FAS), Fetal Alcohol Effects (FAE), and Alcohol Related Neurodevelopmental Disorder (ARND), now referred to as Fetal Alcohol Spectrum Disorders (FASD). I instantly came to realize how little I really knew about alcohol abuse and its potential ramifications beyond the subject of alcoholism. My world view of alcohol abuse and alcoholism was, indeed, very narrow up to the age of 55.
Prior to my first exposure to an FASD case in 1993, I had observed signs posted in establishments that served alcoholic beverages that warned women who were pregnant not to consume alcohol; however, I did not appreciate the reason for the Surgeon General's warning that now appears on all domestic and imported alcoholic beverages containers in the United States. Nor did I have any inkling as to how I would have to adjust my thinking in order to begin to understand the full impact that FASD should and would have on how courts of law function. Mind you, up to this time, I had not heard of Dr. Ann Streissguth, Dr. Susan Astley, Dr. Sterling Clarren and Dr. Robin LaDue, all living and working right in my own community, Seattle, Washington, which is in King County. Nor did I know that Seattle was the center of FAS/FAE research in the United States. And, I certainly didn't know that, through the education that I was about to receive from these very same experts in the years to come, that I would become one of a handful of judicial officers that would have the requisite knowledge to intelligently address audiences through out the world, judges, lawyers, mental health providers, educators, social workers, probation and parole officers, law enforcement officers and family of persons with FASD on issues involving FASD and the judicial system.

My education started one afternoon when a case was called into court for a pre-trial hearing to determine whether a 15 year old was competent to stand trial on a sexual offense. The youngster's lawyer began by explaining to me that I would be hearing testimony from both a psychologist and a medical doctor that his client suffered from FAS. The attorney also informed me that his client's attention span was so poor that it would be necessary for the court to take a recess every 30 minutes, as opposed to our standard of every 90 minutes, so that the in order to explain to the client what had just taken place in the courtroom and to help him refocus his attention on the hearing. The lawyer also indicated that he and the social worker who would be participating in this task would need a very quiet room in order to accomplish this effort. I was told that the quiet environment was necessary due to the fact that the youngster did not handle noise or crowds well because both caused extreme anxiety for him. In fact, the public area at Juvenile Court was, and still is, very noisy and crowded throughout our typical court day. I was immediately struck by the realization that recesses that have always been designed to give the court, its staff, the attorneys, their client and witnesses a mid-morning and mid-afternoon break, suddenly became very important for another reason . . . to accommodate the disability of this young person, so that he alone, could participate in the proceeding against him in a meaningful way, that is so that he could assist his counsel in his defense to the extent that he was competent to do so. This was a strange feeling because judges, through their legal training and experiences, become easily entrenched in doing things — the way they have always been done — and change, when it does occur, comes ever so slowly. The outcome of this case, in the larger scheme of things, is not as important as what was to follow in my development of a full understanding of FASD and the lessons learned. Suffice it to say that the youngster did not qualify as mentally retarded based on his full scale IQ score (few with FASD do so qualify), and the case law in our state did not require much more than a demonstration that the accused knows the colors of the American flag, is oriented to time and place, has at least a minimal understanding of what he was accused of and what are the responsibilities of his lawyer, the prosecutor and the judge. The law at that time did not recognize a difference between mental illness, mental retardation, and FASD. The same standard applied for determining the competency of persons afflicted with these conditions and adaptive behavioral deficits and how they impact competency was not understood or recognized for how they may impact the question of competency.

As a result of this case and another one that came up shortly thereafter, I was asked by the Chief Judge of our Juvenile Court in the Fall of 1993 to organize and chair a multi-disciplinary committee to establish protocols for determining the competency of youth suffering from organic brain damage. FAS and FAE were the primary catalysts for this endeavor. The final report of the committee was submitted to the Chief Judge on March 24, 1994. The composition of the committee included a prosecutor, a public defender, a social worker with one of the public defense agencies, Dr. Sterling Clarren, Dr. Susan Astley, Dr. Robin LaDue, and a representative from the Washington Protection Advocacy organization. This was my first extended learning experience regarding FAS and FAE.
As a result of the committee’s effort and what it produced, I was asked in the Fall of 1994 to serve on an Advisory Panel on FAS/FAE to be established by the then Governor of the State of Washington, Mike Lowry. Shortly after accepting the invitation, I attended the first meeting of the panel which was presided over by the Governor’s wife, serving as the Honorary Chair. Before the meeting ended, I was elected to serve as the permanent chair. The membership was not only a “Who’s Who” of FAS/FAE/ARND experts, Drs. Clarren, Streissguth, and Astley, but also included adoptive parents, representatives from a number of Washington’s Native American tribes, representatives from the March of Dimes, other health care providers, public school and chemical dependency educators, Seattle-King County Public Health, Catholic Community Services, a birth parent and a young adult with FAE. This group was responsible for creating a set of “Recommendations to Governor Lowry” which was submitted in December, 1995. The report led to a number of actions taken by our state legislature over the following years. It also was my first exposure to the enormity of the problems presented by FASD, not only in the judicial arena but also in every other aspect of society, from mental health, to education, law enforcement, family structure and dysfunction, the community, adoption services, and social, and economic services. It also was the impetus for my future endeavors to educate judges, lawyers and others regarding FASD, its impact on the judicial system and society, and how the courts can best respond to individuals with FASD in the justice arena.

For the next several years I took time away from the bench to do presentations at continuing legal education and multi-disciplinary conferences and workshops around the State of Washington on the topic of FAS/FAE/ARND and the courts, always pointing out that, in fact, the reach of these conditions go far beyond just the judicial system. Unfortunately, the demands of the court were such that my assignments in the adult criminal and civil divisions of our court led me to other responsibilities and my involvement in FASD education took a back seat until 2003 when I was contacted by Kay Kelly, Project Manager for the Legal Research Center, a program co-sponsored by the Fetal Alcohol and Drug Unit (FADU) of the University of Washington Medical and Law Schools. Kay introduced herself and indicated that Dr. Streissguth wanted to know what the chance was of Dr. Streissguth and others presenting at a judicial education session to the judges of our state. It was too late to do anything for the up and coming 2003 Annual Washington Judicial Conference. As the Chair of the Supreme Court’s Annual Judicial Conference Education Committee, I told her we should work on it for the following year. In 2004, the first presentation was done. The presenters consisted of Kay Kelly, Professor Eric Schnapper of the University of Washington, School of Law, Dr. (Professor) Ann Streissguth, Judge Carlie Trueman from British Columbia, and me as moderator and a presenter. Dr. Streissguth provided the scientific foundation for a discussion of the legal issues surrounding the primary and secondary disabilities that are typically associated with the brain damage caused by prenatal exposure to alcohol. The presentation was so well received that we were asked to present at the 2005 annual conference on a more limited topic, “Juvenile and Adult Sentencing.”

I had retired from the court after 34 years as a judge in January of 2005. By the time we did the presentation at the 2005 annual judicial conference, Kay had fully entrenched me in my new post-retirement career as a consultant to the FADU and a public advocate for and educator of lawyers, judges and all other interested professional and lay people. Since the spring of 2005, I have presented at a number of conferences and workshops in the States of Washington, Texas, Arizona, and Illinois as well as New Zealand and Australia. In addition, since 2005 I have had the good fortune of being invited back to present at every bi-annual Canadian International Conference, held in Victoria, BC, until April of this year when it had to be moved to Vancouver, BC due to attendance exceeding 1,000 participants. I have also presented at the Canadian National Conferences which are held in Vancouver, BC on the alternating bi-annual years. In addition to conference and workshop presentations, I have written articles that have either been published or are in the works along with power point presentations on various legal subjects dealing with FASD which are listed in the bibliography that follows this article. I presently also serve as the Legal Director of FASDExperts, the first, and presently only, multi-disciplinary FASD forensic diagnostic team in the United States.
Looking back to 1993, so little was known about FASD and there is so much more to be learned in the years ahead. My focus began with a very narrow exploration of the subject of FASD, accommodations of special needs and competency to stand trial. Now, mental retardation protects a person from being put to death for a capital crime and yet persons with FASD, who seldom qualify as mentally retarded, but who often times are more disabled than those afflicted with mental retardation, are still at risk of being put to death for their crimes. Even though our United States Supreme Court has ruled in the case of Atkins v. Virginia, 122 S.Ct. 2242 (June 20, 2002) that a mentally retarded person cannot be put to death, the individual states have been slow to amend their mental retardation laws to conform to the requirements of the Atkins decision.

We have not been successful, as yet, at finding national support for a special set of standards for determining the competency of people with FASD to stand trial for the crimes they are accused of committing, although one federal court now recognizes the need for separate standards for determining competency of people suffering from mental illness and those who suffer from mental retardation. The case is United States v. Duhon, 104 F. Supp. 2d. 663 (W. District of Louisiana, 2000). The principles and considerations discussed by the court in regard to mental retardation are equally applicable to the adaptive behavioral deficits suffered by people as a result of FASD according to Dr. Stephen Greenspan, PhD a renowned expert on mental retardation.

Our judicial and penal systems, including our custodial institutions have yet to understand the need for diagnosis, much less the need to structure support systems and probation and parole services to meet the special needs of this population. This is the case even though, based on Dr. Streissguth's research approximately 60% of youngsters and adults with FASD get in trouble with the law, and, according to Canadian studies of prison populations, upwards of 40 percent of the people populating our penal institutions suffer from FASD.

Finally, our educational systems in the United States continue to fail to understand FASD and the special educational needs of this population. School administrators throughout the United States continue to resist their federally mandated responsibility to provide meaningful education, treating children with FASD as a nuisance and distraction from the effort to educate mainstream students. This has been the case time and time again where experts have provided a firm diagnosis of brain damage and the disabilities caused by pre-natal exposure to alcohol.

As I said at the beginning of this article, things change slowly in the judicial system, and for that matter amongst most of our governmental institutions. I hope that my journey does not end before I have an opportunity to participate in FASD educational endeavors in the United Kingdom, which, I I still find enchanting after taking a year of English History in college some 51 years ago.

Bibliography of and links to articles and power point presentations:

A. Wartnik, "Stopping the Revolving Door of the Justice Systems: Ten Principles for Sentencing and Other Disposition of People with FASD," [www.uwcita.org](http://www.uwcita.org) (Click on Training Materials and then Fetal Alcohol Spectrum Disorders).


A. Wartnik and S. Carlson, "A Judicial Perspective on Issues Impacting the Trial Courts Related to FASD," Journal of Law and Psychiatry (Publication is pending for later this year).

Drs. R. Adler, N. Brown and P. Connor, and A. Wartnik, “Competency to Stand Trial, Diminished Capacity, and Fetal Alcohol Spectrum Disorder,” Journal of Law and Psychiatry (Publication is pending for 2012)

Video and power points presentations may be found at www.fasdexperts.com

Additional power point presentations may be found at www.uwcita.org

Additional power point presentations and other information on the author may be found by googling “FASD – Wartnik”.

A webcast presentation from the 2011 Canadian Fourth International Conference on FASD may be found at www.interprofessional.ubc.ca (In the grey box captioned “Webcast”, click on “here” and then scroll down to the links that read: “FASD: What’s a Judge to do?” and “FASD and the Law: Rethinking the Criminal Justice System” which has six parts. Scroll to the bottom of the page and click on “2” which will take you to screens 3 through 6.

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1) VOLUNTARY EXERCISE INDUCES ADULT HIPPOCAMPAL NEUROGENESIS AND BDNF EXPRESSION IN A RODENT MODEL OF FETAL ALCOHOL SPECTRUM DISORDERS
Boehme F, Gil-Mohapel J, Cox A, Patten A, Giles E, Brocardo PS, Christie BR.
Division of Medical Sciences, Island Medical Program, University of Victoria, Victoria, BC, V8W 2Y2, Canada Department of Biology, University of Victoria, Victoria, BC, Canada Brain Research Centre and Program in Neuroscience, University of British Columbia, Vancouver, BC, Canada Department of Cellular and Physiological Sciences, University of British Columbia, Vancouver, BC, Canada.

ABSTRACT
Alcohol consumption during pregnancy can result in a myriad of health problems in the affected offspring ranging from growth deficiencies to central nervous system impairments that result in cognitive deficits. Adult hippocampal neurogenesis is thought to play a role in cognition (i.e. learning and memory) and can be modulated by extrinsic factors such as alcohol consumption and physical exercise. We examined the impact of voluntary physical exercise on adult hippocampal neurogenesis in a rat model of fetal alcohol spectrum disorders (FASD). Intragastric intubation was used to deliver ethanol to rats in a highly controlled fashion through all three trimester equivalents (i.e. throughout gestation and during the first 10 days of postnatal life). Ethanol-exposed animals and their pair-fed and ad libitum controls were left undisturbed until they reached a young adult stage at which point they had free access to a running wheel for 12 days. Prenatal and early postnatal ethanol exposure altered cell proliferation in young adult female rats and increased early neuronal maturation without affecting cell survival in the dentate gyrus (DG) of the hippocampus. Voluntary wheel running increased cell proliferation, neuronal maturation and cell survival as well as levels of brain-derived neurotrophic factor in the DG of both ethanol-exposed female rats and their pair-fed and ad libitum controls.

These results indicate that the capacity of the brain to respond to exercise is not impaired in this model of FASD, highlighting the potential therapeutic value of physical exercise for this developmental disorder.

Link to the Article,

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2) FIELD TRIAL OF ALCOHOL-SERVER TRAINING FOR PREVENTION OF FETAL ALCOHOL SYNDROME
Dresser J, Starling R, Woodall WG, Stanghetta P, May PA.
Center on Alcoholism, Substance Abuse, and Addictions, University of New Mexico, 2650 Yale Boulevard SE, Albuquerque, New Mexico 87106.

ABSTRACT
Objective: An alcohol-server training program to prevent fetal alcohol syndrome was developed, implemented, and evaluated in a comparison study of public drinking establishments in New Mexico and Oregon.
Method: The management and serving staffs of 148 establishments licensed for on-premise alcohol sales in the two states studied were trained to discourage alcohol consumption by pregnant customers. Pre- and post-tests of server responses to pregnant-appearing "pseudo-patron" actors ordering alcohol in experimental (n = 148) and comparison (n = 183) establishments were a key method of evaluating the efficacy of this intervention.

Results: Within-group chi-square analyses compared rates of service refusal at baseline with 1-month, 6-month, and 12-month follow-up points for both the trained (experimental) and the comparison establishments. No differences were found between experimental and comparison establishments at baseline at either site, but significant differences were found for New Mexico at each posttraining measurement point. In Oregon, the refusal rate at baseline increased from 1.5% at baseline to 8.3% at 1 month, which only approached significance. In New Mexico, at baseline the refusal rate was 8.6%, and it rose to 39.2% at 6 months (p < .0001, odds ratio = 6.83) and remained high at 28.2% at 12 months (p < .001, odds ratio = 4.15). No similarly significant gains were recorded at control establishments.

Conclusions: Supplemental responsible beverage service training for alcohol servers to aid in the prevention of fetal alcohol exposure can be effective in reducing the serving of alcohol to visibly pregnant women, with robust effects continuing over the subsequent year in the New Mexico establishments.


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PubMed, Alcohol Alcohol. 2011 Apr 22

3) WHAT DO WE KNOW ABOUT THE ECONOMIC IMPACT OF FETAL ALCOHOL SPECTRUM DISORDER? A SYSTEMATIC LITERATURE REVIEW
Popova S, Stade B, Bekmuradov D, Lange S, Rehm J.
Social and Epidemiological Research Department, Centre for Addiction and Mental Health
33 Russell St., Toronto, ON, Canada M5S 2S1

ABSTRACT
Aims: The objective of this study was to conduct a systematic review of the literature related to the measurement of the economic impact of Fetal Alcohol Spectrum Disorder (FASD) in different countries and to categorize the available literature.

Methods: A systematic literature search of the studies concerning the economic impact of FASD was conducted using multiple electronic bibliographic databases.

Results: The literature on the economic burden of FASD is scarce. There are a limited number of studies found in Canada and the USA, and data from the rest of the world are absent. Existing estimates of the economic impact of FASD demonstrate significant cost implications on the individual, the family and society. However, these estimates vary considerably due to the different methodologies used by different studies.

Conclusion: Limitations and gaps in the existing methodologies of calculating the economic costs of FASD are discussed. It is evident that there is an urgent need to develop a comprehensive and sound...
methodology for calculating the economic impact of FASD to the society.


4) A TRANSIENT PLACENTAL SOURCE OF SEROTONIN FOR THE FETAL FOREBRAIN
Alexandre Bonnin, Nick Goeden, Kevin Chen, Melissa L. Wilson, Jennifer King, Jean C. Shih, Randy D. Blakely, Evan S. Deneris & Pat Levitt

ABSTRACT
Serotonin (5-hydroxytryptamine or 5-HT) is thought to regulate neurodevelopmental processes through maternal–fetal interactions that have long-term mental health implications. It is thought that beyond fetal 5-HT neurons there are significant maternal contributions to fetal 5-HT during pregnancy1, 2 but this has not been tested empirically. To examine putative central and peripheral sources of embryonic brain 5-HT, we used Pet1−/− (also called Fev) mice in which most dorsal raphe neurons lack 5-HT3. We detected previously unknown differences in accumulation of 5-HT between the forebrain and hindbrain during early and late fetal stages, through an exogenous source of 5-HT which is not of maternal origin. Using additional genetic strategies, a new technology for studying placental biology ex vivo and direct manipulation of placental neosynthesis, we investigated the nature of this exogenous source. We uncovered a placental 5-HT synthetic pathway from a maternal tryptophan precursor in both mice and humans. This study reveals a new, direct role for placental metabolic pathways in modulating fetal brain development and indicates that maternal–placental–fetal interactions could underlie the pronounced impact of 5-HT on long-lasting mental health outcomes.

Read Full Article, http://www.nature.com/nature/journal/v472/n7343/full/nature09972.html

5) FETAL ALCOHOL SPECTRUM DISORDERS: NEUROPSYCHOLOGICAL AND BEHAVIORAL FEATURES
Mattson SN, Crocker N, Nguyen TT

ABSTRACT
Heavy prenatal alcohol exposure can cause alterations to the developing brain. The resulting neurobehavioral deficits seen following this exposure are wide-ranging and potentially devastating and, therefore, are of significant concern to individuals, families, communities, and society. These effects occur on a continuum, and qualitatively similar neuropsychological and behavioral features are seen across the spectrum of effect. The term fetal alcohol spectrum disorders (FASD) has been used to emphasize the continuous nature of the outcomes of prenatal alcohol exposure, with fetal alcohol syndrome (FAS) representing one point on the spectrum.

This paper will provide a comprehensive review of the neuropsychological and behavioral effects of heavy prenatal alcohol exposure, including a discussion of the emerging neurobehavioral profile.
Supporting studies of lower levels of exposure, brain-behavior associations, and animal model systems will be included when appropriate.

**Link to the Article,**
[http://www.unboundmedicine.com/medline/ebm/record/21503685/abstract/Fetal_Alcohol_Spectrum_Disorders:_Neuropsychological_and_Behavioral_Features](http://www.unboundmedicine.com/medline/ebm/record/21503685/abstract/Fetal_Alcohol_Spectrum_Disorders:_Neuropsychological_and_Behavioral_Features)

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6) **THE EFFECTS OF PRENATAL ALCOHOL EXPOSURE ON BEHAVIOR: RODENT AND PRIMATE STUDIES**
Schneider ML, Moore CF, Adkins MM.
Harlow Center for Biological Psychology, University of Wisconsin-Madison, 22 North Charter Street, Madison, WI, 53715, USA, schneider@education.wisc.edu.

**ABSTRACT**
The use of alcohol by women during pregnancy is a continuing problem. In this review the behavioral effects of prenatal alcohol from animal models are described and related to studies of children and adults with FASD. Studies with monkeys and rodents show that prenatal alcohol exposure adversely affects neonatal orienting, attention and motor maturity, as well as activity level, executive function, response inhibition, and sensory processing later in life. The primate moderate dose behavioral findings fill an important gap between human correlational data and rodent mechanistic research. These animal findings are directly translatable to human findings. Moreover, primate studies that manipulated prenatal alcohol exposure and prenatal stress independently show that prenatal stress exacerbates prenatal alcohol-induced behavioral impairments, underscoring the need to consider stress-induced effects in fetal alcohol research. Studies in rodents and primates show long-term effects of prenatal and developmental alcohol exposure on dopamine system functioning, which could underpin the behavioral effects.

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7) **CAMKII ACTIVATION IS A NOVEL EFFECTOR OF ALCOHOL’S NEUROTOXICITY IN NEURAL CREST STEM/PROGENITOR CELLS**
Garic A, Flentke GR, Amberger E, Hernandez M, Smith SM.
Waisman Center for Developmental Disabilities Department of Nutritional Sciences, University of Wisconsin-Madison, 1415 Linden Drive, Madison WI 53706.

**ABSTRACT**
Prenatal ethanol exposure causes significant neurodevelopmental deficits through its induction of apoptosis in neuronal progenitors including the neural crest. Using an established chick embryo model, we previously showed that clinically relevant ethanol concentrations cause neural crest apoptosis through mobilization of an intracellular calcium transient. How the calcium transient initiates this cell death is unknown. Here we identify CaMKII as the calcium target responsible for ethanol-induced apoptosis. Immunostaining revealed selective enrichment of activated
phosphoCaMKII(Thr286) within ethanol-treated neural crest. CaMKII activation in response to ethanol was rapid (<60 sec) and robust, and CaMKII activity was increased 300% over control levels. Treatment with CaMKII-selective inhibitors but not those directed against CaMKIV or PKC completely prevented the cell death. Forced expression of dominant-negative CaMKII prevented ethanol's activation of CaMKII and prevented the ethanol-induced death, whereas constitutively-active CaMKII in ethanol's absence significantly increased cell death to levels caused by ethanol treatment. In summary, CaMKII is the key signal that converts the ethanol-induced, short-lived Ca(i) (2+) transient into a long-lived cellular effector. This is the first identification of CaMKII as a critical mediator of ethanol-induced cell death. Because neural crest differentiates into several neuronal lineages, our findings offer novel insights into how ethanol disrupts early neurogenesis.

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8) FETAL ALCOHOL SPECTRUM DISORDERS: AN OVERVIEW
Riley EP, Infante MA, Warren KR.
Department of Psychology, Center for Behavioral Teratology, San Diego State University, 6330 Alvarado Court, Suite 100, San Diego, CA, 92120, USA, eriley@mail.sdsu.edu.

ABSTRACT
When fetal alcohol syndrome (FAS) was initially described, diagnosis was based upon physical parameters including facial anomalies and growth retardation, with evidence of developmental delay or mental deficiency. Forty years of research has shown that FAS lies towards the extreme end of what are now termed fetal alcohol spectrum disorders (FASD). The most profound effects of prenatal alcohol exposure are on the developing brain and the cognitive and behavioral effects that ensue. Alcohol exposure affects brain development via numerous pathways at all stages from neurogenesis to myelination. For example, the same processes that give rise to the facial characteristics of FAS also cause abnormal brain development. Behaviors as diverse as executive functioning to motor control are affected. This special issue of Neuropsychology Review addresses these changes in brain and behavior highlighting the relationship between the two. A diagnostic goal is to recognize FAS as a disorder of brain rather than one of physical characteristics.

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9) FUNCTIONAL NEUROIMAGING IN THE EXAMINATION OF EFFECTS OF PRENATAL ALCOHOL EXPOSURE
Coles CD, Li Z.
Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 1256 Briarcliff Rd, NE, Atlanta, GA, 30306, USA, ccoles@emory.edu

ABSTRACT
Functional neuroimaging offers the opportunity to understand the effect of prenatal alcohol exposure...
on the activities of the brain as well as providing a window into the relationship between neural activation and the behavioral outcomes that have been described in affected individuals. Several different methodologies have been used to examine the neurophysiological signal changes associated with different brain functions in prenatally exposed individuals and those diagnosed with fetal alcohol syndrome (FAS) or other fetal alcohol spectrum disorders (FASD). These include electroencephalography (EEG), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI). These studies demonstrate that it is feasible to use these technologies with this clinical population and that the damage to the central nervous system associated with prenatal alcohol exposure has widespread functional implications; however, currently, the literature in these areas is limited and unsystematic. Functional MRI with this clinical population has just begun to explore the implications of prenatal alcohol exposure with the first paper published in 2005. Other methodologies are similarly limited in scope. Nonetheless, these functional neuroimaging studies suggest that prenatal alcohol exposure, or a diagnosis of FAS, may lead to restrictions in neural efficiency or a global decrement in processing resources.

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PubMed, Brain Res. 2011 Apr 12;1384:29-41.

10) ALTERED ADULT HIPPOCAMPAL NEURONAL MATURATION IN A RAT MODEL OF FETAL ALCOHOL SYNDROME
Gil-Mohapel J, Boehme F, Patten A, Cox A, Kainer L, Giles E, Brocardo PS, Christie BR.
Division of Medical Sciences, Island Medical Program, University of Victoria, Victoria, British Columbia, Canada.

ABSTRACT
Exposure to ethanol during pregnancy can be devastating to the developing nervous system, leading to significant central nervous system dysfunction. The hippocampus, one of the two brain regions where neurogenesis persists into adulthood, is particularly sensitive to the teratogenic effects of ethanol. In the present study, we tested a rat model of fetal alcohol syndrome (FAS) with ethanol administered via gavage throughout all three trimester equivalents. Subsequently, we assessed cell proliferation, as well as neuronal survival, and differentiation in the dentate gyrus of the hippocampus of adolescent (35days old), young adult (60days old) and adult (90days old) Sprague-Dawley rats. Using both extrinsic (bromodeoxyuridine) and intrinsic (Ki-67) markers, we observed no significant alterations in cell proliferation and survival in ethanol-exposed animals when compared with their pair-fed and ad libitum controls. However, we detected a significant increase in the number of new immature neurons in animals that were exposed to ethanol throughout all three trimester equivalents. This result might reflect a compensatory mechanism to counteract the deleterious effects of prenatal ethanol exposure or an ethanol-induced arrest of the neurogenic process at the early neuronal maturation stages. Taken together these results indicate that exposure to ethanol during the period of brain development causes a long-lasting dysregulation of the neurogenic process, a mechanism that might contribute, at least in part, to the hippocampal deficits that have been reported in rodent models of FAS.

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11) CLINICAL AND PATHOLOGICAL FEATURES OF ALCOHOL-RELATED BRAIN DAMAGE
Zahr NM, Kaufman KL, Harper CG.
Department of Psychiatry and Behavioral Sciences, 401 Quarry Road, Stanford University, Stanford, CA 94305, USA.

ABSTRACT
One of the sequelae of chronic alcohol abuse is malnutrition. Importantly, a deficiency in thiamine (vitamin B(1)) can result in the acute, potentially reversible neurological disorder Wernicke encephalopathy (WE). When WE is recognized, thiamine treatment can elicit a rapid clinical recovery. If WE is left untreated, however, patients can develop Korsakoff syndrome (KS), a severe neurological disorder characterized by anterograde amnesia. Alcohol-related brain damage (ARBD) describes the effects of chronic alcohol consumption on human brain structure and function in the absence of more discrete and well-characterized neurological concomitants of alcoholism such as WE and KS. Through knowledge of both the well-described changes in brain structure and function that are evident in alcohol-related disorders such as WE and KS and the clinical outcomes associated with these changes, researchers have begun to gain a better understanding of ARBD. This Review examines ARBD from the perspective of WE and KS, exploring the clinical presentations, postmortem brain pathology, in vivo MRI findings and potential molecular mechanisms associated with these conditions. An awareness of the consequences of chronic alcohol consumption on human behavior and brain structure can enable clinicians to improve detection and treatment of ARBD.


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12) PREVALENCE, PREDICTORS AND PERINATAL OUTCOMES OF PERI-CONCEPTIONAL ALCOHOL EXPOSURE - RETROSPECTIVE COHORT STUDY IN AN URBAN OBSTETRIC POPULATION IN IRELAND
Mullally A, Cleary BJ, Barry J, Fahey TP, Murphy DJ.
Academic Department of Obstetrics & Gynaecology, Coombe Women and Infants University Hospital & Trinity College Dublin, Dublin 8, Republic of Ireland. deirdre.j.murphy@tcd.ie.

ABSTRACT
Background: Evidence-based advice on alcohol consumption is required for pregnant women and women planning a pregnancy. Our aim was to investigate the prevalence, predictors and perinatal outcomes associated with peri-conceptional alcohol consumption.

Methods: A cohort study of 61,241 women who booked for antenatal care and delivered in a large urban maternity hospital between 2000 and 2007. Self-reported alcohol consumption at the booking visit was categorised as low (0-5 units per week), moderate (6-20 units per week) and high (>20 units per week).

Results: Of the 81% of women who reported alcohol consumption during the peri-conceptional period, 71% reported low intake, 9.9% moderate intake and 0.2% high intake. Factors associated with moderate alcohol consumption included being in employment OR 4.47 (95% CI 4.17 to 4.80), Irish nationality OR 16.5 (95% CI 14.9 to 18.3), private health care OR 5.83 (95% CI 5.38 to 6.31) and smoking OR 1.86 (95% CI 1.73 to 2.01). Factors associated with high consumption included maternal
age less than 25 years OR 2.70 (95% CI 1.86 to 3.91) and illicit drug use OR 6.46 (95% CI 3.32 to 12.60). High consumption was associated with very preterm birth (<32 weeks gestation) even after controlling for socio-demographic factors, adjusted OR 3.15 (95% CI 1.26-7.88). Only three cases of Fetal Alcohol Syndrome were recorded (0.05 per 1000 total births), one each in the low, moderate and high consumption groups.

Conclusions: Public Health campaigns need to emphasise the importance of peri-conceptional health and pre-pregnancy planning. Fetal Alcohol Syndrome is likely to be under-reported despite the high prevalence of alcohol consumption in this population.


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13) EARLY HEALTH CARE UTILIZATION AND WELFARE INTERVENTIONS AMONG CHILDREN OF MOTHERS WITH ALCOHOL AND SUBSTANCE ABUSE: A RETROSPECTIVE COHORT STUDY
Children's Hospital, University of Helsinki and Helsinki University Central Hospital, POB 281, FIN-00029 HUCH, Helsinki, Finland
THL National Institute for Health and Welfare, POB 30, FIN-00271, Helsinki, Finland and Nordic School of Public Health, Gothenburg, Sweden Department of Obstetrics and Gynecology, Helsinki University Central Hospital, POB 140, FIN-00029 HUCH, Helsinki, Finland
The Social Insurance Institution (SII), Research Department, Nordenskiöldinkatu 12, FIN-00250, Helsinki, Finland.

ABSTRACT
Aim: Early childhood health care utilization, mortality, and welfare interventions were studied among children of mothers with identified gestational alcohol and/or substance abuse.

Methods: Register based retrospective cohort study. The exposed cohort consisted of 638 children born to 524 women followed-up antenatally 1992-2001 at special outpatient clinics in the capital area of Finland. Non-exposed children (n=1914) born to control women were matched for maternal age, parity, number of fetuses, month of birth, and delivery hospital of the index child. Postnatal data of both cohorts was collected from national registers until 2007.

Results: The exposed cohort displayed twice the amount of in- and outpatient hospital care episodes compared with non-exposed children. Differences attributable to exposure were found in categories of conditions originating in the perinatal period, mental and behavioural disorders, and non-specific factors influencing health status and contact with health services. This was reflected in amounts of reimbursements for drugs of the central nervous system, as well as special care allowances and rehabilitation for mental and behavioural disorders. The highest degree of health care utilization was observed among exposed children placed in out-of-home care. One third of these children received outpatient care and one tenth required inpatient care for a mental and behavioral disorder. No significant differences were found in early mortality.

Conclusion: The exposed children displayed significant neonatal and early mental and behavioural
health care utilization, and need for significant psychosocial support during their first decade of life.

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14) CANADIAN PALPEBRAL FISSURE LENGTH GROWTH CHARTS REFLECT A GOOD FIT FOR TWO SCHOOL AND FASD CLINIC-BASED U.S. POPULATIONS
Susan J Astley

ABSTRACT
Background: Short palpebral fissure lengths (PFL) are one of three facial features that define the unique facial phenotype of fetal alcohol syndrome (FAS). Published PFL growth charts vary greatly in both rate and magnitude of growth, placing their accuracy and validity in question. New PFL growth charts were recently published to reflect a racial/ethnic cross section of Canadian girls and boys 6-16 years of age. PFLs were measured from digital facial photographs using the FAS Facial Photographic Analysis Software.

Objectives: Assess the goodness of fit of two U.S. populations (healthy children and children with prenatal alcohol exposure) when plotted on the Canadian, Hall, and other published PFL charts.

Methods: The PFLs of 106 healthy children and 822 children with prenatal alcohol exposure from Washington State were measured from digital facial photographs using the FAS Facial Photographic Analysis Software. Goodness of fit was assessed graphically and by computation of the mean PFL z-score.

Results: Our predominantly Caucasian, healthy group of children scattered along the mean growth curve on the Canadian charts (mean PFL z-score +0.2), and fell 1.6 SDs below the mean on the Hall chart (mean PFL z-score -1.6). The mean PFL z-score for the children with FAS was 2.4 SDs below the mean on the Canadian charts and 3.9 SDs below the mean on the Hall chart. African Americans were not a good fit.

Conclusion: The Canadian PFL charts were a good fit for our predominantly Caucasian populations of healthy U.S. school-aged children. Children with FAS continued to present with PFLs 2 or more SDs below the mean when plotted on the Canadian PFL charts, supporting the FAS PFL diagnostic criteria used by the FASD 4-Digit Diagnostic Code. Use of PFL charts normed for African Americans is recommended. Updated PFL charts for 0-6 years of age are vital to prevent an artificial over-estimation of short PFLs in this age group.

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http://www.cjcp.ca/pubmed.php?articleId=316

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15) A WEB-BASED INNOVATION TO REDUCE ALCOHOL-EXPOSED PREGNANCIES IN THE COMMUNITY
Tenkku LE, Mengel MB, Nicholson RA, Hile MG, Morris DS, Salas J.

ABSTRACT
Despite warnings that drinking during pregnancy is unsafe, many women are still at risk for an alcohol-exposed pregnancy (AEP). This article describes the outcomes of a web-based, self-guided change intervention designed to lower the risk for AEPs in a community. A sample of 458 women, between the ages of 18 and 44 years and at risk for an AEP (i.e., any drinking in the past 30 days and not using reliable contraception), participated in the study. A total of 58% of the women enrolled in the self-guided change intervention were no longer at risk for an AEP at the 4-month follow-up. Sublevel analysis revealed that mail and online versions of the intervention were equally successful at reducing risk for an AEP. This study represents a successful implementation of a web-based, self-guided change intervention to reduce risk for an AEP, an intervention with community-wide reach due to the Internet platform.

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16) GEOGRAPHIC AND MATERNAL CHARACTERISTICS ASSOCIATED WITH ALCOHOL USE IN PREGNANCY
Burns L, Black E, Powers JR, Loxton D, Elliott E, Shakeshaft A, Dunlop A.
From the National Drug and Alcohol Research Centre (LB, EB, AS), University of New South Wales, Sydney, Australia; Priority Research Centre for Gender, Health and Ageing (JRP, DL), University of Newcastle, Callaghan, Australia; Discipline of Paediatrics and Child Health (EE), University of Sydney, Sydney, Australia; Hunter New England Area Health Service (AD), Newcastle, Australia.

ABSTRACT
Background: To date, no studies have used population-level data to investigate whether maternal location of residence (metropolitan vs. regional/remote populations) is associated with alcohol use in pregnancy. This information has important implications for appropriate service provision.

Methods: Information on all live births in New South Wales Australia was linked to records of alcohol-related admissions for mothers of these births over a 6-year period (2000 to 2006). Cases were women who had at least 1 alcohol-related hospital admission during pregnancy or at birth. Controls were women who had at least 1 live birth over that same time period but no alcohol-related hospital admissions during that time. Admissions were considered to be alcohol-related based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM) code. Demographic, obstetric, and neonatal variables were compared.

Results: A total of 417,464 singleton birth records were analyzed, 488 of which were coded positive for at least 1 alcohol-related ICD-10-AM diagnosis. Characteristics associated with alcohol-related admissions in pregnancy were residence in a remote/very remote area, being Australian-born, having had a previous pregnancy, smoking in the current pregnancy, and presenting late to antenatal care. Alcohol-exposed pregnancies were associated with a range of poor obstetric and neonatal outcomes,
with no geographic differences noted. However, women in regional/remote areas were less likely to attend specialist obstetric hospitals.

**Conclusions:** This study shows the need for standardized screening programs for alcohol use in pregnancy and where problematic use is detected, for clear clinical guidelines on management and referral.

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**17) THE EFFECTIVENESS OF A COMMUNITY-BASED INTERVENTION FOR PARENTS WITH FASD**
Denys K, Rasmussen C, Henneveld D.
Department of Pediatrics, University of Alberta, Glenrose Rehabilitation Hospital, 10230-111 Ave., Edmonton, AB, Canada. kennedydenys@gmail.com

**ABSTRACT**
The purpose of this study was to evaluate the effectiveness of the Step by Step program in which mentors work with parents affected by Fetal Alcohol Spectrum Disorder (FASD) on a one-to-one basis. Mentors help clients identify and work towards meeting their needs and achieving their goals. Data from 24 closed client files was collected and analyzed and as predicted, the program was effective in helping clients reduce their needs and achieve their goals. The clients' reason for leaving the program as well as whether or not they had a formal FASD diagnosis had an impact on their success in the program. Data collected on additional mental health issues, experience of abuse and addictions helped to characterize the sample of clients and correlations were found between clients' experience of abuse and their past and/or present addictions issues. Limitations of this study as well as future implications were also discussed.

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**18) SUBSTANCE USE IN PREGNANCY**
Wong S, Ordean A, Kahan M.
Toronto ON.

**ABSTRACT**
**Objective:** To improve awareness and knowledge of problematic substance use in pregnancy and to provide evidence-based recommendations for the management of this challenging clinical issue for all health care providers.

**Options:** This guideline reviews the use of screening tools, general approach to care, and recommendations for clinical management of problematic substance use in pregnancy.

www.nofas-uk.org
Outcomes: Evidence-based recommendations for screening and management of problematic substance use during pregnancy and lactation.

Evidence: Medline, PubMed, CINAHL, and The Cochrane Library were searched for articles published from 1950 using the following key words: substance-related disorders, mass screening, pregnancy complications, pregnancy, prenatal care, cocaine, cannabis, methadone, opioid, tobacco, nicotine, solvents, hallucinogens, and amphetamines. Results were initially restricted to systematic reviews and randomized control trials/controlled clinical trials. A subsequent search for observational studies was also conducted because there are few RCTs in this field of study. Articles were restricted to human studies published in English.

Additional articles were located by hand searching through article reference lists. Searches were updated on a regular basis and incorporated in the guideline up to December 2009. Grey (unpublished) literature was also identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies. Values: The quality of evidence was rated using the criteria described in the Report of the Canadian Task Force on the Preventive Health Care. Recommendations for practice were ranked according to the method described in that report (Table 1). Benefits, harms, and costs: This guideline is intended to increase the knowledge and comfort level of health care providers caring for pregnant women who have substance use disorders. Improved access to health care and assistance with appropriate addiction care leads to reduced health care costs and decreased maternal and neonatal morbidity and mortality.

Recommendations

1. All pregnant women and women of childbearing age should be screened periodically for alcohol, tobacco, and prescription and illicit drug use. (III-A)
2. When testing for substance use is clinically indicated, urine drug screening is the preferred method. (II-2A) Informed consent should be obtained from the woman before maternal drug toxicology testing is ordered. (III-B)
3. Policies and legal requirements with respect to drug testing of newborns may vary by jurisdiction, and caregivers should be familiar with the regulations in their region. (III-A)
4. Health care providers should employ a flexible approach to the care of women who have substance use problems, and they should encourage the use of all available community resources. (II-2B)
5. Women should be counselled about the risks of periconception, antepartum, and postpartum drug use. (III-B)
6. Smoking cessation counselling should be considered as a first-line intervention for pregnant smokers. (I-A)
7. Methadone maintenance treatment should be standard of care for opioid-dependent women during pregnancy. (II-IA) Other slow-release opioid preparations may be considered if methadone is not available. (II-2B)
8. Opioid detoxification should be reserved for selected women because of the high risk of relapse to opioids. (II-2B)
9. Opiate-dependent women should be informed that neonates exposed to heroin, prescription opioids, methadone, or buprenorphine during pregnancy are monitored closely for symptoms and signs of neonatal withdrawal (neonatal abstinence syndrome). (II-2B)
10. Antenatal planning for intrapartum and postpartum analgesia may be offered for all women in consultation with appropriate health care providers. (III-B)
11. The risks and benefits of breastfeeding should be weighed on an individual basis because methadone maintenance therapy is not a contraindication to breastfeeding. (II-3B).

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19) AWARENESS AND KNOWLEDGE ABOUT RISKS OF DRINKING DURING PREGNANCY IN PREGNANT LEBANESE WOMEN
Département de psychiatrie, hôpital psychiatrique de la Croix, Jall-Eddib, faculté de médecine, USJ, BP 60096, Liban.

ABSTRACT
Objective: To assess the awareness and knowledge of pregnant Lebanese women about the risks of drinking during pregnancy and the factors that influence their drinking patterns.

Materials and methods: A prospective study was conducted on a sample of 107 women consulting the gynecology outpatient department of Hôtel-Dieu de France in Beirut, Lebanon, who completed the T-ACE screening test included in a 21 multiple choice questionnaire which examine knowledge and beliefs about alcohol use during pregnancy, drinking patterns and awareness of fetal alcohol exposure.

Results: The 107 women of our sample were all married, between 20 and 41 years old and had mostly a high educational level (86%). Most of the women (47%) were at their first pregnancy. Of the 20 women who self-reported drinking during pregnancy, 60% obtained a positive score on the T-ACE questionnaire, which indicates that more than 11% of the women engaged with potentially high risk drinking for the baby. There is not a significant difference between the different age categories or educational levels. This proportion is lower than that found in international publications. However, the rate of excessive drinking (4 drinks or more on any one occasion in females) was higher and one woman in five reported excessive drinking in the previous year. There is a high level of knowledge that alcohol use during pregnancy is harmful to the child, and the more consumption the more harmful and likely the effects, but there is confusion about the safety of small amounts of alcohol. Women (37%) think that there is a safe level of drinking during pregnancy; 29% tolerate up to one drink a month, 9% tolerate up to one drink a week and one woman thinks having one drink a day is safe. Women who actually drink during pregnancy are more likely to think that alcohol consumption to a certain level is safe. Women (31%) think that beer and/or wine are safe alcohols to a certain level during pregnancy. When asked about the source of this belief, 22% mention a gynecologist but the majority (61%) says it is a personal belief. Women (65%) in our sample are aware that alcohol use during pregnancy can lead to life-long disabilities in a child, such as delayed development (36%), birth defects/deformities (35%) and mental retardation (32%). However, up to 33% of the respondents report having no information about the effects of alcohol on the fetus and two women believe alcohol is not harmful at all. Women with lower levels of education are somewhat less knowledgeable about the risks of alcohol use during pregnancy than those with higher levels of education. There is no association between the drinking patterns of the women with their age, their professional habits and the alcohol consumption of their husbands. The women in our sample seem to be more aware of the necessity to stop smoking rather than stop drinking during pregnancy.

Conclusion: Lebanese women are not fully aware of the recommendations and risks related to drinking during pregnancy. This is the reason why action must be taken to ensure better diffusion of these recommendations and better assessment of alcohol intake during prenatal visits.

THE ROLE OF OXIDATIVE STRESS IN FETAL ALCOHOL SPECTRUM DISORDERS
Brocardo PS, Gil-Mohapel J, Christie BR.
Division of Medical Sciences, University of Victoria, Victoria, BC, V8W 2Y2, Canada.

ABSTRACT
The ingestion of alcohol/ethanol during pregnancy can result in abnormal fetal development in both humans and a variety of experimental animal models. Depending on the pattern of consumption, the dose, and the period of exposure to ethanol, a myriad of structural and functional deficits can be observed. These teratogenic effects are thought to result from the ethanol-induced dysregulation of a variety of intracellular pathways ultimately culminating in toxicity and cell death. For instance, ethanol exposure can lead to the generation of reactive oxygen species (ROS) and produce an imbalance in the intracellular redox state, leading to an overall increase in oxidative stress. In the present review we will provide an up-to-date summary on the effects of prenatal/neonatal ethanol exposure on the levels of oxidative stress in the central nervous system (CNS) of experimental models of fetal alcohol spectrum disorders (FASD). We will also review the evidence for the use of antioxidants as potential therapeutic strategies for the treatment of some of the neuropathological deficits characteristic of both rodent models of FASD and children afflicted with these disorders. We conclude that an imbalance in the intracellular redox state contributes to the deficits seen in FASD and suggest that antioxidants are potential candidates for the development of novel therapeutic strategies for the treatment of these developmental disorders.

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TERATOGENIC EFFECTS OF ETHANOL VAPOUR EXPOSURE ON CHICK EMBRYOS
Kiran Kamran  (Department of Anatomy, Foundation University Medical College, Islamabad)
Muhammad Yunus Khan  (Regional Center, College of Physician & Surgeons, Islamabad.)
Liaqatali Minhas  (Yusra Medical & Dental College, Islamabad)

ABSTRACT
Objective: To observe the effect of ethanol vapours on chick embryos regarding developmental defects and hatchability characteristics.

Methods: An experimental study was performed in the Department of Anatomy at the Regional Center of College of Physicians and Surgeons, Islamabad, from February, 2006 to February, 2007. Chicken eggs after having been exposed to ethanol vapours produced in a specially designed glass chamber, were dissected on day 7, day 10 and day 22 or on hatching and compared with age-matched controls. A breathalyzer was used for monitoring level of ethanol vapours inside the incubator.

Results: The results show that experimental group had comparatively more cases of delayed and assisted hatchings as well as growth retardation resulting into failure of retraction of yolk sac, as compared to the controls.

Conclusion: Ethanol vapour exposure increases the risks of developmental defects with increasing
embryonic age. Increased duration of exposure, causes delayed hatching and more assisted hatchings. Newly hatched alcohol exposed chicks showed diminished locomotor activity and poor balance.

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22) PAEDIATRICIANS' KNOWLEDGE, ATTITUDES AND PRACTICE FOLLOWING PROVISION OF EDUCATIONAL RESOURCES ABOUT PREVENTION OF PRENATAL ALCOHOL EXPOSURE AND FETAL ALCOHOL SPECTRUM DISORDER
Payne JM, France KE, Henley N, D'Antoine HA, Bartu AE, Mutch RC, Elliott EJ, Bower C. Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia, Perth Centre for Applied Social Marketing Research, Edith Cowan University, Perth School of Nursing and Midwifery, Curtin Health Innovation Research Institute, Curtin University of Technology, Perth, Western Australia Discipline of Paediatrics and Child Health, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia.

ABSTRACT

Aim: The study aims to provide paediatricians in Western Australia (WA) with educational resources (http://www.ichr.uwa.edu.au/alcoholandpregnancy) about the prevention of prenatal alcohol exposure and fetal alcohol spectrum disorder, and assess changes in their knowledge, attitudes and practice about fetal alcohol syndrome (FAS) and alcohol consumption in pregnancy.

Methods: Following our 2004 survey of paediatricians, we developed and distributed educational resources to 159 paediatricians in WA in 2007. Six months later, we surveyed these paediatricians and compared their responses with results from 2004 using prevalence rate ratios (PRRs) and 95% confidence intervals (CIs).

Results: Of 133 eligible paediatricians, 82 (61.7%) responded: 65.9% had seen the resources, of these 66.7% had used them and 29.6% said the resources had helped them change, or influenced their intent to change, their practice. There was no change in the proportion that knew all the essential features of FAS (18.3% in 2007; 20.0% in 2004) or had diagnosed FAS (58.5% in 2007; 58.9% in 2004). An increased proportion (75.6% in 2007; 48.9% in 2004) agreed that pregnant women should completely abstain from consuming alcohol (PRR 1.55, 95% CI 1.21-1.97). Only 21.7% (no increase from 2004) routinely asked about alcohol use when taking a pregnancy history.

Conclusions: We recommend that asking about alcohol use during pregnancy should be emphasised in paediatric training. Unless paediatricians' capacity to ask about alcohol consumption when taking a pregnancy history and to diagnose FAS is increased, FAS will remain under-diagnosed in Australia and opportunities for management, early intervention and prevention will be overlooked.


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23) **MAGNETIC RESONANCE-BASED IMAGING IN ANIMAL MODELS OF FETAL ALCOHOL SPECTRUM DISORDER**

O'Leary-Moore SK, Parnell SE, Lipinski RJ, Sulik KK.
Bowles Center for Alcohol Studies, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599, USA, somoore@med.unc.edu.

**ABSTRACT**

Magnetic resonance imaging (MRI) techniques, such as magnetic resonance microscopy (MRM), diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS), have recently been applied to the study of both normal and abnormal structure and neurochemistry in small animals. Herein, findings from studies in which these methods have been used for the examination of animal models of Fetal Alcohol Spectrum Disorder (FASD) are discussed. Emphasis is placed on results of imaging studies in fetal and postnatal mice that have highlighted the developmental stage dependency of prenatal ethanol exposure-induced CNS defects. Consideration is also given to the promise of methodological advances to allow in vivo studies of aberrant brain and behavior relationships in model animals and to the translational nature of this work.


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24) **PEDAGOGICALLY BEREFT! IMPROVING LEARNING OUTCOMES FOR CHILDREN WITH FOETAL ALCOHOL SPECTRUM DISORDERS**

Professor Barry Carpenter

**ABSTRACT**

Foetal alcohol spectrum disorder (FASD) is the most common non-genetic cause of learning disability, affecting around 1% of live births in Europe, and costing an estimated $2.9 million per individual across their lifespan. In adulthood, non-reversible brain damage is often compounded by secondary disabilities in adulthood, such as mental health problems and drug addiction. The challenge for today's educators is: How do we teach children with FASD? Their unusual style of learning and their extreme challenging behaviour is out of the experience of many teachers. This article, written by Professor Barry Carpenter, OBE, National Director of the Specialist Schools & Academies Trust Complex Learning Difficulties and Disabilities Research Project, considers the status of FASD in the UK, and provides an overview of the author's recent research into effective educational strategies within the framework of Every Child Matters. Only government-led approaches can lead to improvements in the quality of teaching and learning for children with FASD and their future life chances.


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25) SI-RNA INHIBITION OF BRAIN INSULIN OR INSULIN-LIKE GROWTH FACTOR RECEPTORS CAUSES DEVELOPMENTAL CEREBELLAR ABNORMALITIES: RELEVANCE TO FETAL ALCOHOL SPECTRUM DISORDER
De la Monte SM, Tong M, Bowling N, Moskal P.
Department of Pathology and Division of Neuropathology, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903 USA. Suzanne_delamonte_md@Brown.edu

ABSTRACT
Background: In experimental models of fetal alcohol spectrum disorder (FASD), cerebellar hypoplasia and hypofoliation are associated with insulin and insulin-like growth factor (IGF) resistance with impaired signaling through pathways that mediate growth, survival, plasticity, metabolism, and neurotransmitter function. To more directly assess the roles of impaired insulin and IGF signaling during brain development, we administered intracerebroventricular (ICV) injections of si-RNA targeting the insulin receptor, (InR), IGF-1 receptor (IGF-1R), or IGF-2R into postnatal day 2 (P2) Long Evans rat pups and examined the sustained effects on cerebellar function, structure, and neurotransmitter-related gene expression (P20).

Results: Rotarod tests on P20 demonstrated significant impairments in motor function, and histological studies revealed pronounced cerebellar hypotrophy, hypoplasia, and hypofoliation in si-InR, si-IGF-1R, and si-IGF-2R treated rats. Quantitative RT-PCR analysis showed that si-InR, and to a lesser extent si-IGF-2R, broadly inhibited expression of insulin and IGF-2 polypeptides, and insulin, IGF-1, and IGF-2 receptors in the brain. ELISA studies showed that si-InR increased cerebellar levels of tau, phospho-tau and β-actin, and inhibited GAPDH. In addition, si-InR, si-IGF-1R, and si-IGF-2R inhibited expression of choline acetyltransferase, which mediates motor function. Although the ICV si-RNA treatments generally spared the neurotrophin and neurotrophin receptor expression, si-InR and si-IGF-1R inhibited NT3, while si-IGF-1R suppressed BDNF.

Conclusions: Early postnatal inhibition of brain InR expression, and to lesser extents, IGF-R, causes structural and functional abnormalities that resemble effects of FASD. The findings suggest that major abnormalities in brains with FASD are mediated by impairments in insulin/IGF signaling. Potential therapeutic strategies to reduce the long-term impact of prenatal alcohol exposure may include treatment with agents that restore brain insulin and IGF responsiveness.


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26) EPIDEMIOLOGICAL STUDY ON ADDICTIVE BEHAVIOURS DURING PREGNANCY IN A UNIVERSITY DEPARTMENT
Service d'addictologie, hôpital Jaint-Jacques, CHU de Nantes, 85, rue Saint-Jacques, 44093 Nantes cedex 1, France.

ABSTRACT
Object: Epidemiological study on addictive disorders during pregnancy.
Methods: An epidemiological study about addictive disorders has been led in the maternity of the University Hospital of Nantes in 2008 on a sample of 300 women, just after childbirth. The prevalence of consumption of drugs was assessed on declared consumption of legal and illegal substances and on the Fagerström questionnaire, the AUDIT questionnaire and the CAST questionnaire. Diagnostic of eating disorders was based on DSM IV criteria of mental anorexia and bulimia nervosa.

Results: At the beginning of pregnancy, 34% of women used tobacco, 63% alcohol and 8% cannabis. Among the women of the study 0.7% had criteria for mental anorexia, 2.3% for bulimia nervosa and 9% for sub clinic forms. After the first trimester, 22% of women declared using tobacco, 20% alcohol and 3% cannabis. The use of various drugs during pregnancy concerned 6.3% of women, and 38% used at least one drug after the first trimester.

Conclusion: The high prevalence of addictive disorders during pregnancy should incite professional of prenatal care to improve their screening methodology and not only when tobacco or alcohol is suspected.


ABSTRACT
Objective: Neuroprotective peptides (NAP+SAL) can prevent some alcohol-induced damage in fetal alcohol syndrome (FAS). Fractalkine, a chemokine constitutively expressed in the CNS reduces neuronal death from activated microglia. Using a model of FAS we evaluated if fractalkine is altered and if NAP+SAL work through fractalkine.

Study Design: Using a FAS model, C57BL6/J-mice were treated on gestational day 8 with alcohol (0.03 mL/g), placebo or alcohol+peptides. Embryos were harvested after 6h(E8) and 10 days later(E18). Fractalkine was measured in the protein lysate (Luminex xMAP). Statistical analysis included Kruskal-Wallis.

Results: Fractalkine was significantly elevated at 6h (median 341pg/ml, range 263-424pg/ml) vs. controls (median 228pg/ml, range 146-332pg/ml; P<.001). NAP+SAL prevented the alcohol-induced increase (median 137, range 97-255 pg/ml, P<.001). At E18, fractalkine levels were similar in all groups (P=0.7).

Conclusion: Prenatal alcohol exposure acutely elevates fractalkine, perhaps in an effort to counter the alcohol toxicity. Pre-treatment with NAP+SAL prevents the acute increase in fractalkine.

28) ETHANOL, ACETALDEHYDE, AND ESTRADIOL AFFECT GROWTH AND DIFFERENTIATION OF RHESUS MONKEY EMBRYONIC STEM CELLS

Vandevoort CA, Hill DL, Chaffin CL, Conley AJ.
From the California National Primate Research Center (CAV, DLH), Davis, California; Department of Obstetrics and Gynecology (GAV), University of California, Davis, Davis, California; Department of OB/GYN & Reproductive Sciences (CLC), University of Maryland School of Medicine, Baltimore, Maryland; Department of Population, Health and Reproduction (AJC), University of California, Davis, Davis, California.

ABSTRACT
Background: The timing of the origins of fetal alcohol syndrome has been difficult to determine, in part because of the challenge associated with in vivo studies of the peri-implantation stage of embryonic development. Because embryonic stem cells (ESCs) are derived from blastocyst stage embryos, they are used as a model for early embryo development.

Methods: Rhesus monkey ESC lines (ORMES-6 and ORMES-7) were treated with 0, 0.01, 0.1, or 1.0% ethanol, 1.0% ethanol with estradiol, or 0.00025% acetaldehyde with or without estradiol for 4 weeks.

Results: Although control ESCs remained unchanged, abnormal morphology of ESCs in the ethanol and acetaldehyde treatment groups was observed before 2 weeks of treatment. Immunofluorescence staining of key pluripotency markers (TRA-1-81 and alkaline phosphatase) indicated a loss of ESC pluripotency in the 1.0% ethanol group. ORMES-7 was more sensitive to effects of ethanol than ORMES-6.

Conclusions: Estradiol appeared to increase sensitivity to ethanol in the ORMES-6 and ORMES-7 cell line. The morphological changes and labeling for pluripotency, proliferation, and apoptosis demonstrated that how ethanol affects these early cells that develop in culture, their differentiation state in particular. The effects of ethanol may be mediated in part through metabolic pathways regulating acetaldehyde formation, and while potentially accentuated by estradiol in some individuals, how remains to be determined.


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ABSTRACT
Prenatal exposure to alcohol is thought to be the most prevalent nongenetic cause of a wide range of neurodevelopmental deficits. Insufficient thyroid hormone levels are one mechanism that hampers development of the alcohol-exposed brain, and we hypothesized that altered dosage of the imprinted thyroid hormone-inactivating gene deiodinase-III (Dio3) is responsible. To follow parent-of-origin allelic expression of Dio3 in the fetal and adult offspring of alcohol-consuming and control dams, we reciprocally crossed 2 polymorphic rat strains. In the frontal cortex, prenatal alcohol exposure altered imprinting patterns and total expression of Dio3 in the fetus and produced a permanent hypothyroid milieu in the adult. In the hippocampus, alcohol affected the paternal and total expression of Dio3 in the fetus and in the adult male, where thyroid hormone levels were concomitantly increased. Hippocampus-dependent behavioral deficits were identified exclusively in males, suggesting they are dependent on aberrant allelic Dio3 expression. None of these effects were observed in offspring of the reciprocal cross. Thus, genetic background and sex modify vulnerability to prenatal alcohol via brain region-specific expression of Dio3. This finding implies that phenotypic heterogeneity in human fetal alcohol spectrum disorder can be linked to genetic vulnerability in affected brain regions.—Sittig, L. J., Shukla, P. K., Herzing, L. B. K., Redei, E. E. Strain-specific vulnerability to alcohol exposure in utero via hippocampal parent-of-origin expression of deiodinase-III.

Read Full Article,
http://www.fasebj.org/content/early/2011/03/22/fj.10-179234.abstract


30) TISSUE PLASMINOGEN ACTIVATOR IS REQUIRED FOR THE DEVELOPMENT OF FETAL ALCOHOL SYNDROME IN MICE
Noel M, Norris EH, Strickland S.
Laboratory of Neurobiology and Genetics, The Rockefeller University, New York, NY 10065.

ABSTRACT
Ethanol exposure during developmental synaptogenesis can lead to brain defects referred to as fetal alcohol syndrome (FAS), which can include mental health problems such as cognitive deficits and mental retardation. In FAS, widespread neuronal death and brain mass loss precedes behavioral and cognitive impairments in adulthood. Because tissue plasminogen activator (tPA) has been implicated in neurodegeneration, we examined whether it mediates FAS. Neonatal WT and tPA(-/-) mice were injected with ethanol to mimic FAS in humans. In WT mice, ethanol elicited caspase-3 activation, significant forebrain neurodegeneration, and decreased contextual fear conditioning in adults. However, tPA-deficient mice were protected from these neurotoxicities, and this protection could be abrogated by exogenous tPA. Selective pharmacological modulators of NMDA and GABA(A) receptor pathways revealed that the effects of tPA were mediated by the NR2B subunit of the NMDA receptor. This study identifies tPA as a critical signaling component in FAS.

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TROPHIC AND PROLIFERATIVE PERTURBATIONS OF IN VIVO/IN VITRO CEPHALIC NEURAL CREST CELLS AFTER ETHANOL EXPOSURE ARE PREVENTED BY NEUROTROPHIN 3

Jaurena MB, Carri NG, Battiato NL, Rovasio RA.

ABSTRACT
Neural crest cells (NCCs), a transient population that migrates from the developing neural tube, distributes through the embryo and differentiates into many derivatives, are clearly involved in the damage induced by prenatal exposure to ethanol. The aim of this work was to evaluate alterations of trophic parameters of in vivo (in ovo) and in vitro NCCs exposed to teratogenic ethanol doses, and their possible prevention by trophic factor treatment. Chick embryos of 24-30h of incubation were treated during 10h with 100mM ethanol, or 40ng/ml Neurotrophin 3 (NT3), or 10ng/ml Ciliary Neurotrophic Factor (CNTF), or ethanol plus NT3 or CNTF, or defined medium; then the topographic distribution of NCC apoptosis was assessed using a whole-mount acridine orange supravital method. Cultures of cephalic NCCs were exposed to the same ethanol or NT3, or CNTF treatments, or ethanol plus one of both trophic factors, or N2 medium. A viability assay was performed using the calcein-ethidium test, apoptosis was evaluated with the TUNEL test, and proliferative capacity after BrdU labeling. After direct exposure of embryos to 100mM ethanol for 10h, a high level of NCC apoptosis was coincident with the abnormal closure of the neural tube. These anomalies were prevented in embryos exposed to ethanol plus NT3 but not with CNTF. In NCC cultures, high cell mortality and a diminution of proliferative activity were observed after 3h of ethanol treatment. Incubation with ethanol plus NT3 (but not with CNTF) prevented NCC mortality as well as a fall in NCC proliferation. The consequences of direct exposure to ethanol expand data from our and other laboratories, supporting current opinion on the potential risk of alcohol ingestion (even at low doses and/or during a short time), in any period of pregnancy or lactation. Our in vivo/in vitro model encourages us to examine the pathogenic mechanism(s) of the ethanol-exposed embryo as well as the use of trophic factors for the treatment and/or prevention of anomalies induced by prenatal alcohol.

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ANTAGONISM OF OREXIN 1 RECEPTORS ELIMINATES MOTOR HYPERACTIVITY AND IMPROVES HOMING RESPONSE ACQUISITION IN JUVENILE RATS EXPOSED TO ALCOHOL DURING EARLY POSTNATAL PERIOD

Stettner GM, Kubin L, Volgin DV.
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ABSTRACT
Consequences of prenatal alcohol exposure (AE) include motor hyperactivity, disrupted sleep and cognitive deficits. Hypothalamic orexin (ORX)-synthesizing neurons are important for the maintenance of vigilance and regulation of motor activity but their hyperactivity may contribute to anxiety disorders. Using a rat model, we tested whether ORX plays a role in behavioral consequences of prenatal AE. Male rat pups received 2.625g/kg of alcohol (AE group) intragastrically twice daily on postnatal days
(PD)4-9, a developmental period equivalent to the third trimester of human pregnancy. Control pups were sham-intubated (S group). On PD12-14, they received daily injections of either the ORX-1 receptor antagonist, SB-334867 (SB; 20mg/kg, i.p.) or vehicle (V) during the lights-off period. On PD16, they were subjected to the homing response (HR) test. On PD17, their motor activity was monitored in a novel environment. The percentage of tests in which HR acquisition was not achieved and the number of trials needed to reach the shortest HR latency were higher, whereas the percentage of successful trials was lower, in AE-V than in S-V rats (p=0.0009-0.03). In contrast, these measures were not significantly different between AE-SB and either S-SB or S-V rats. Motor activity in AE-V rats was significantly higher than in S-V (p=0.003), S-SB (p=0.007) or AE-SB (p=0.02) rats, with no difference between S-SB and AE-SB group. Our findings suggest that excessive activity of ORX neurons contributes to motor hyperactivity and impaired HR acquisition following perinatal AE and that these symptoms may be alleviated by systemic antagonism of ORX-1 receptors.

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21 March 2011

33) EFFECTS OF PRENATAL ETHANOL EXPOSURE ON RAT BRAIN RADIAL GLIA AND NEUROBLAST MIGRATION
Aronne MP, Guadagnoli T, Fontanet P, Evrard SG, Brusco A.

ABSTRACT
Prenatal ethanol exposure (PEE) induces morphologic and functional alterations in the developing central nervous system. The orderly migration of neuroblasts is a key process in the development of a layered structure such as the cerebral cortex (CC). From initial stages of corticogenesis, the transcription factor Pax6 is intensely expressed in neuroepithelial and radial glia cells (RGCs) and is involved in continual regulation of cell surface properties responsible for both cellular identity and radial migration. In the present work, one month before mating, during pregnancy and lactation, a group of female Wistar rats were fed a liquid diet with 5.9% (w/w) ethanol (EtOH), rendering moderate blood EtOH concentrations. Maternal gestational weight progression and fetal CC thickness were measured. CC from E12-P3 rats were examined for expression of vimentin, nestin, S-100b, Pax6 and doublecortin using immunohistochemical assays. RGCs expressing vimentin, nestin, S-100b and Pax6 had abnormal morphologies. The migration distance through the CC and the number of doublecortin-ir neuroblasts in germinative zones were decreased. We found significant morphologic defects on RGCs, a marked delay in neuronal migration, decreased numbers of neuroblasts, and decreased numbers of Pax6-ir cells in the CC as a consequence of exposure to ethanol during development. These observations suggest a sequence of toxic events that contribute to cortical dysplasia in offspring exposed to EtOH during gestation.

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34) REGIONAL BRAIN VOLUME REDUCTIONS RELATE TO FACIAL DYSMORPHOLOGY AND NEUROCOGNITIVE FUNCTION IN FETAL ALCOHOL SPECTRUM DISORDERS
Roussotte FF, Sulik KK, Mattson SN, Riley EP, Jones KL, Adnams CM, May PA, O'Connor MJ, Narr KL, Sowell ER

ABSTRACT
Individually with heavy prenatal alcohol exposure can experience significant deficits in cognitive and psychosocial functioning and alterations in brain structure that persist into adulthood. In this report, data from 99 participants collected across three sites (Los Angeles and San Diego, California, and Cape Town, South Africa) were analyzed to examine relationships between brain structure, neurocognitive function, facial morphology, and maternal reports of quantities of alcohol consumption during the first trimester. Across study sites, we found highly significant volume reductions in the FASD group for all of the brain regions evaluated. After correcting for scan location, age, and total brain volume, these differences remained significant in some regions of the basal ganglia and diencephalon. In alcohol-exposed subjects, we found that smaller palpebral fissures were significantly associated with reduced volumes in the ventral diencephalon bilaterally, that greater dysmorphology of the philtrum predicted smaller volumes in basal ganglia and diencephalic structures, and that lower IQ scores were associated with both smaller basal ganglia volumes and greater facial dysmorphology. In subjects from South Africa, we found a significant negative correlation between intracranial volume and total number of drinks per week in the first trimester. These results corroborate previous reports that prenatal alcohol exposure is particularly toxic to basal ganglia and diencephalic structures. We extend previous findings by illustrating relationships between specific measures of facial dysmorphology and the volumes of particular subcortical structures, and for the first time show that continuous measures of maternal alcohol consumption during the first trimester relates to overall brain volume reduction. Hum Brain Mapp, 2011.

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http://www.unboundmedicine.com/medline/ebm/record/21416562/abstract/Regional_brain_volume_reductions_relate_to_facial_dysmorphology_and_neurocognitive_function_in_fetal_alcohol_spectrum_disorders

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35) MODERATE FETAL ALCOHOL EXPOSURE IMPAIRS NEUROGENIC CAPACITY OF MURINE NEURAL STEM CELLS ISOLATED FROM THE ADULT SUBVENTRICULAR ZONE
Roitbak T, Thomas K, Martin A, Allan A, Cunningham LA.

ABSTRACT
Gestational alcohol exposure leads to a spectrum of neurological symptoms which range from severe mental retardation caused by high dose exposure, to subtle cognitive and neuropsychiatric symptoms caused by low-to-moderate doses. We and other investigators have demonstrated that exposure to moderate levels of alcohol throughout gestation leads to impaired neurogenesis in the adult hippocampus, although the mechanisms by which this occurs are not known. To begin to distinguish cell-intrinsic from microenvironmental contributions to impaired adult neurogenesis, we isolated neural stem progenitor cells (NSPCs) from the adult SVZ of mice exposed to moderate levels of alcohol throughout gestation. We found that NSPCs isolated from fetal alcohol exposed (FAE) mice displayed reduced neurosphere formation in culture, as assessed by a serial passage neurosphere assay, and reduced neuronal differentiation upon growth factor withdrawal. These studies suggest that gestational
alcohol exposure leads to long-lasting NSPC-intrinsic dysregulation, which may underlie in vivo neurogenic deficits.


36) EFFECTS OF ETHANOL ON TRANSFORMING GROWTH FACTOR B1-DEPENDENT AND -INDEPENDENT MECHANISMS OF NEURAL STEM CELL APOPTOSIS
Hicks SD, Miller MW.
Department of Neuroscience and Physiology, State University of New York, Upstate Medical University, Syracuse, NY 13210, USA.

ABSTRACT
Stem cell vitality is critical for the growth of the developing brain. Growth factors can define the survival of neural stem cells (NSCs) and ethanol can affect growth factor-mediated activities. The present study tested two hypotheses: (a) ethanol causes the apoptotic death of NSCs and (b) this effect is influenced by the ambient growth factor. Monolayer cultures of non-immortalized NS-5 cells were exposed to fibroblast growth factor (FGF) 2 or transforming growth factor (TGF) β1 in the absence or presence of ethanol for 48h. Ethanol killed NSCs as measured by increases in the numbers of ethidium bromide+ and annexin V+ cells and decreases in the number of calcein AM+ (viable) cells. These toxic effects were promoted by TGFβ1. A quantitative polymerase chain reaction array of apoptosis-related mRNAs revealed an ethanol-induced increase (≥2-fold change; p<0.05) in transcripts involved in Fas ligand (FasL) and tumor necrosis factor (TNF) signaling. These effects, particularly the FasL pathway, were potentiated by TGFβ1. Immunocytochemical analyses of NS-5 cells showed that transcriptional alterations translated into consistent up-regulation of protein expression. Experiments with the neocortical proliferative zones harvested from fetal mice exposed to ethanol showed that ethanol activated similar molecular systems in vivo. Thus, ethanol induces NSC death through two distinct molecular mechanisms, one is initiated by TGFβ1 (FasL) and another (through TNF) which is TGFβ1-independent.


37) WEB-BASED ASSESSMENT AND BRIEF INTERVENTION FOR ALCOHOL USE IN WOMEN OF CHILDBEARING POTENTIAL: A REPORT OF THE PRIMARY FINDINGS
From the Domestic Division/Underage Drinking Prevention Education Initiatives (KD-H), University Research Company, LLC, Bethesda, Maryland; Department of Pediatrics and Department of Family and Preventive Medicine (CDC), University of California, San Diego, La Jolla, California; School of Social Work (JDC), San Diego State University, San Diego, California; Department of Mathematics (RX, KD), University of California, San Diego, La Jolla, California; Counseling and Psychological

www.nofas-uk.org
ABSTRACT

Background: There is a need for more effective assessment and primary prevention programs aimed at accurately measuring and reducing alcohol consumption among women before conception in underserved, high-risk populations. Health information technology may serve this purpose; however, the effectiveness of such tools within this population is not known.

Methods: We conducted a small-scale randomized controlled trial to test the effectiveness of an adapted web-based alcohol assessment and intervention tool among low-income, nonpregnant women of reproductive age who were receiving Women Infant and Children (WIC) services in San Diego County and who reported currently drinking at a moderate risk level. A total of 150 risky drinking participants completed a web-based assessment and were randomly assigned to either receive a personalized feedback intervention or general health information about alcohol consumption and fetal alcohol syndrome. Follow-up assessments on reported alcohol consumption were conducted via telephone at 1- and 2-months postbaseline. Participants ranged in age from 18 to 44 and were predominately Hispanic/Latina (44%).

Results: At baseline, all respondents reported consuming ≥3 standard drinks on ≥1 occasion in the previous month. Outcome data were available for 131 participants. The main outcome measure was reduction in the number of risky drinking occasions, which did not differ significantly between treatment conditions (odds ratio 1.200, 95% CI 0.567 to 2.539, p = 0.634). Over 70% of the participants, however, reported a reduction in risky drinking occasions regardless of treatment condition (control 43/63, 68%; experimental 49/68, 72%).

Conclusions: The results of this study demonstrate that web-based assessment of alcohol consumption among low-income women of reproductive age, as represented by WIC clients, is feasible and acceptable. The findings also suggest that detailed and interactive assessments of alcohol consumption may be sufficient for the reduction of risky drinking within this population without personalized feedback.

assessed in a whole embryo culture beginning on embryonic day 8.25, with or without alcohol administration at 88 mM for 6 hours followed by 42 hours culture in ethanol-free media.

**Results:** Contrasting strain differences in susceptibility were observed for the brain, the face, and other organ systems using the Maele-Fabry and Picard scoring system. The forebrain, midbrain, hindbrain, heart, optic vesicle, caudal neural tube, and hindlimbs of the B6 mice were severely delayed in growth, whereas compared to the respective controls, only the forebrain and optic vesicle were delayed in the D2 mice, and no effects were found in the 129S6 mice. A large number of cleaved (c)-caspase 3 positive (+) cells were found in regions of the brain, optic vesicles, cranial nerve nuclei V, VII, VIII, and IX as well as the craniofacial primordial; only a few were found in corresponding regions of the B6 controls. In contrast, only a small number of c-caspase 3 immunostaining cells were found in either the alcohol treated or the controls of the D2 embryos and in 129S6 embryos. The independent apoptotic markers TUNEL and Nile blue staining further confirmed the strain differences in apoptotic responses in both the neural tube and craniofacial primordia.

**Conclusions:** Under embryo culture conditions, in which alcohol exposure factors and fetal developmental staging were controlled, and maternal and intrauterine factors were eliminated, the degree of growth retardation and the extent and type of neurodevelopmental teratogenesis varied significantly across strains. Notably, the 129S6 strain was remarkably resistant to alcohol-induced growth deficits, confirming a previous in vivo study, and the D2 strain was also significantly less affected than the B6 strain. These findings demonstrate that fetal genotype is an important factor that can contribute to the variation in fetal alcohol spectrum disorder.

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39) **COMPARISON OF VERBAL LEARNING AND MEMORY IN CHILDREN WITH HEAVY PRENATAL ALCOHOL EXPOSURE OR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER**
Crocker N, Vaurio L, Riley EP, Mattson SN.
From the Center for Behavioral Teratology, Department of Psychology, San Diego State University, San Diego, California.

**ABSTRACT**
**Background:** Children with fetal alcohol spectrum disorders (FASD) have deficits in verbal learning and recall. However, the specificity of these deficits has not been adequately tested. In the current study, verbal learning and memory performance of children with heavy prenatal alcohol exposure was compared to children with attention-deficit/hyperactivity disorder (ADHD), a disorder commonly seen in alcohol-exposed children.

**Methods:** Performance on the California Verbal Learning Test-Children's Version (CVLT-C) was examined in 3 groups of children (N = 22/group): (i) heavy prenatal alcohol exposure and ADHD (ALC), (ii) nonexposed with ADHD (ADHD), and (iii) nonexposed typically developing (CON). Groups were matched on age, sex, race, ethnicity, handedness, and socioeconomic status (SES).

**Results:** Group differences were noted on learning trials (CON > ADHD > ALC). On the delayed recall trial, CON children performed better than both clinical groups, who did not differ from each other. Children in the ALC group demonstrated poorer recognition than children in the CON and ADHD groups, who did not differ from each other. Marginally significant group differences were noted on retention of previously learned material. Post hoc analyses indicated that ADHD children showed
worse retention relative to the CON group, whereas retention in the ALC children remained intact.

**Conclusions:** These data suggest that children with heavy prenatal alcohol exposure and nonexposed children with ADHD show differential patterns of deficit on the CVLT-C. Performance of alcohol-exposed children reflects inefficient encoding of verbal material, whereas performance of the ADHD group may be better characterized by a deficit in retrieval of learned material. Differences noted between clinical groups add to a growing neurobehavioral profile of FASD that may aid in differential diagnosis.


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40) BEST FRIENDS AND ALCOHOL USE IN ADOLESCENCE: THE ROLE OF THE DOPAMINE D4 RECEPTOR GENE
Hashimoto-Torii K, Kawasawa YI, Kuhn A, Rakic P.
Department of Neurobiology and Kavli Institute for Neuroscience, Yale University School of Medicine, New Haven, CT 06510, USA. Kazue.Hashimoto-Torii@yale.edu

**ABSTRACT**
Fetal exposure to environmental insults increases the susceptibility to late-onset neuropsychiatric disorders. Alcohol is listed as one of such prenatal environmental risk factors and known to exert devastating teratogenic effects on the developing brain, leading to complex neurological and psychiatric symptoms observed in fetal alcohol spectrum disorder (FASD). Here, we performed a coordinated transcriptome analysis of human and mouse fetal cerebral cortices exposed to ethanol in vitro and in vivo, respectively. Up- and down-regulated genes conserved in the human and mouse models and the biological annotation of their expression profiles included many genes/terms related to neural development, such as cell proliferation, neuronal migration and differentiation, providing a reliable connection between the two species. Our data indicate that use of the combined rodent and human model systems provides an effective strategy to reveal and analyze gene expression changes inflicted by various physical and chemical environmental exposures during prenatal development. It also can potentially provide insight into the pathogenesis of environmentally caused brain disorders in humans.


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41) COMBINED TRANSCRIPTOME ANALYSIS OF FETAL HUMAN AND MOUSE CEREBRAL CORTEX EXPOSED TO ALCOHOL
Hashimoto-Torii K, Kawasawa YI, Kuhn A, Rakic P.
Department of Neurobiology and Kavli Institute for Neuroscience, Yale University School of Medicine, New Haven, CT 06510, USA. Kazue.Hashimoto-Torii@yale.edu

**ABSTRACT**
Fetal exposure to environmental insults increases the susceptibility to late-onset neuropsychiatric
disorders. Alcohol is listed as one of such prenatal environmental risk factors and known to exert devastating teratogenic effects on the developing brain, leading to complex neurological and psychiatric symptoms observed in fetal alcohol spectrum disorder (FASD). Here, we performed a coordinated transcriptome analysis of human and mouse fetal cerebral cortices exposed to ethanol in vitro and in vivo, respectively. Up- and down-regulated genes conserved in the human and mouse models and the biological annotation of their expression profiles included many genes/terms related to neural development, such as cell proliferation, neuronal migration and differentiation, providing a reliable connection between the two species. Our data indicate that use of the combined rodent and human model systems provides an effective strategy to reveal and analyze gene expression changes inflicted by various physical and chemical environmental exposures during prenatal development. It also can potentially provide insight into the pathogenesis of environmentally caused brain disorders in humans.

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PubMed, Neuroscientist. 2011 Mar 7

42) FETAL ALCOHOL SPECTRUM DISORDERS AND ABNORMAL NEURONAL PLASTICITY  
Medina AE.  
Department of Anatomy and Neurobiology, Virginia Commonwealth University, School of Medicine, Richmond, VA.

ABSTRACT  
The ingestion of alcohol during pregnancy can result in a group of neurobehavioral abnormalities collectively known as fetal alcohol spectrum disorders (FASD). During the past decade, studies using animal models indicated that early alcohol exposure can dramatically affect neuronal plasticity, an essential property of the central nervous system responsible for the normal wiring of the brain and involved in processes such as learning and memory. The abnormalities in neuronal plasticity caused by alcohol can explain many of the neurobehavioral deficits observed in FASD. Conversely, improving neuronal plasticity may have important therapeutic benefits. In this review, the author discuss the mechanisms that lead to these abnormalities and comment on recent pharmacological approaches that have been showing promising results in improving neuronal plasticity in FASD.

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43) PRENATAL EXPOSURE TO ETHANOL: A SPECIFIC EFFECT ON THE H19 GENE IN SPERM  
Stouder C, Somm E, Paoloni-Giacobino A.  
Department of Genetic and Laboratory Medicine, Geneva University Hospital, 1211 Geneva 14, Switzerland.

ABSTRACT  
Alcohol exposure during pregnancy induces a range of disorders in the offspring. Methylation changes in imprinted genes may play a role in the teratogenic effects of alcohol. We evaluated the possible
effects of alcohol administration in pregnant mice on the methylation pattern of 5 imprinted genes (H19, Gtl2, Peg1, Snrpn and Peg3) in somatic and sperm cell DNAs of the male offspring. The effects observed were a 3% (p<0.005) decrease in the number of methylated CpGs of H19 in the F1 offspring sperm, a 4% (p<0.005) decrease in the number of methylated CpGs of H19 in the F2 offspring brain and a 26% (p<0.05) decrease in the mean sperm concentration. CpGs 1 and 2 of the H19 CTCF-binding site 2 exhibited significant methylation percentage losses. H19 CTCF-binding sites are important for the regulation of Igf2 gene expression. The hypomethylation of H19 may contribute to the decreased spermatogenesis in the offspring.

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44) RESVERATROL PREVENTS ALCOHOL-INDUCED COGNITIVE DEFICITS AND BRAIN DAMAGE BY BLOCKING INFLAMMATORY SIGNALING AND CELL DEATH CASCADE IN NEONATAL RAT BRAIN

Tiwari V, Chopra K.
Pharmacology Research Laboratory, University Institute of Pharmaceutical Sciences, UGC Center of Advanced Study, Panjab University, Chandigarh, India.

ABSTRACT
Human prenatal ethanol exposure that occurs during a period of increased synaptogenesis known as the 'brain growth spurt' has been associated with significant impairments in attention, learning and memory. Recent studies have shown that administration of ethanol to infant rats during the synaptogenesis period (first 2 weeks after birth) triggers extensive apoptotic neurodegeneration throughout many regions of the developing brain and results in cognitive dysfunctions as the animal matures. The present study was designed with an aim to investigate the effect of resveratroil, a polyphenolic phytoalexin (trans-3,5,4-trihydroxy stilbene) present in red wine on alcohol-induced cognitive deficits and neuronal apoptosis in rat pups postnatally exposed to ethanol. Pups were administered ethanol (5 g/kg, 12% v/v) by intragastric intubation on postnatal days 7, 8, and 9.

Ethanol-exposed pups showed impaired memory performance in both Morris water maze elevated plus maze task recorded by using computer tracking with EthoVision software. Behavioral deficit in ethanol-exposed pups was associated with enhanced acetylcholinesterase activity, increased oxidative-nitrosative stress, cytokine (TNF-α, IL-1β and TGF-β), nuclear factor kappa beta and caspase 3 levels in both cerebral cortex and hippocampus. Chronic treatment with resveratroil (10 and 20 mg/kg) significantly attenuated all the behavioral, biochemical and molecular changes in different brain regions of ethanol administered pups. The major finding of the study is that resveratroil blocks activation of nuclear factor kappa beta pathway and apoptotic signaling and prevents cognitive deficits in rats postnatally exposed to ethanol.

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45) EFFECTS OF LIPOIC ACID ON ANTIAPOPTOTIC GENES IN CONTROL AND ETHANOL-TREATED FETAL RHOMBENCEPHALIC NEURONS
Antonio AM, Gillespie RA, Druse-Manteuffel MJ.
Graduate Program in Cell Biology, Neurobiology, and Anatomy, Loyola University Chicago-Stritch School of Medicine, 2160 S. First Avenue, Maywood, IL 60153, USA; The Alcohol Research Program, Loyola University Chicago-Stritch School of Medicine, 2160 S. First Avenue, Maywood, IL 60153, USA.

ABSTRACT
This laboratory showed that ethanol augments apoptosis in fetal rhombencephalic neurons and co-treatment with alpha-lipoic acid (LA) or one of several other antioxidants prevents ethanol-associated apoptosis. Because ethanol increases oxidative stress, which causes apoptosis, it is likely that some of the neuroprotective effects of LA and other antioxidants involve classical antioxidant actions. Considering the reported link of LA with pro-survival cell signaling, it is also possible that LA's neuroprotective effects involve additional mechanisms. The present study investigated the effects of LA on ethanol-treated fetal rhombencephalic neurons with regard to oxidative stress and up-regulation of the pro-survival genes Xiap and Bcl-2. We included parallel gene expression studies with N-acetyl cysteine (NAC) to determine whether LA's effects on Xiap and Bcl-2 were shared by other antioxidants. We also used enzyme inhibitors to determine which signaling pathway(s) might be involved with the effects of LA. The results of this investigation showed that LA treatment of ethanol-treated neurons exerted several pro-survival effects. LA blocked two pro-apoptotic changes, i.e., the ethanol-associated rise in ROS and caspase-3. LA also up-regulated the expression genes that encode the anti-apoptotic proteins Bcl-2 and Xiap by a mechanism that involves NF-κB. NAC also up-regulated Bcl-2 and Xiap. Thus, the neuroprotective effects of LA and NAC could involve up-regulation of pro-survival genes as well as their classical antioxidant actions.


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46) IMAGING THE IMPACT OF PRENATAL ALCOHOL EXPOSURE ON THE STRUCTURE OF THE DEVELOPING HUMAN BRAIN
Lebel C, Roussotte F, Sowell ER.
Developmental Cognitive Neuroimaging Laboratory, Department of Neurology, University of California, 10833 Le Conte Ave, Room 16-131, Los Angeles, CA, 90095-7332, USA, clebel@ucla.edu.

ABSTRACT
Prenatal alcohol exposure has numerous effects on the developing brain, including damage to selective brain structure. We review structural magnetic resonance imaging (MRI) studies of brain abnormalities in subjects prenatally exposed to alcohol. The most common findings include reduced brain volume and malformations of the corpus callosum. Advanced methods have been able to detect shape, thickness and displacement changes throughout multiple brain regions. The teratogenic effects of alcohol appear to be widespread, affecting almost the entire brain. The only region that appears to be relatively spared is the occipital lobe. More recent studies have linked cognition to the underlying brain structure in alcohol-exposed subjects, and several report patterns in the severity of brain damage as it relates to facial dysmorphology or to extent of alcohol exposure. Future studies exploring
relationships between brain structure, cognitive measures, dysmorphology, age, and other variables will be valuable for further comprehending the vast effects of prenatal alcohol exposure and for evaluating possible interventions.


47) TWO ALCOHOL BINDING RESIDUES INTERACT ACROSS A DOMAIN INTERFACE OF THE L1 NEURAL CELL ADHESION MOLECULE AND REGULATE CELL ADHESION
Dou X, Menkari CE, Shanmugasundararaj S, Miller KW, Charness ME.
Harvard Medical School, United States;

ABSTRACT
Ethanol may cause fetal alcohol spectrum disorders (FASD) in part by inhibiting cell adhesion mediated by the L1 neural cell adhesion molecule. Azalcohols photolabel Glu-33 and Tyr-418, two residues that are predicted by homology modeling to lie within 2.8 Å of each other at the interface between the Ig1 and Ig4 domains of L1 (PNAS 105, 371 (2008)). Using transient transfection of NIH/3T3 cells with wild type (WT-L1) and mutated L1, we found that cysteine substitution of both residues (E33C/Y418C-L1) significantly increased L1 adhesion above levels observed for WT-L1 or the single cysteine substitutions E33C-L1 or Y418C-L1. The reducing agent β-mercaptoethanol (βME) reversibly decreased the adhesion of E33C/Y418C-L1, but had no effect on WT-L1, E33C-L1 or Y418C-L1. Thus, disulfide bond formation occurs between Cys-33 and Cys-418, confirming both the close proximity of these residues and the importance of Ig1-Ig4 interactions in L1 adhesion. Maximal ethanol inhibition of cell adhesion was significantly lower in cells expressing E33C/Y418C-L1 than in those expressing WT-L1, E33C-L1, or Y418C-L1. Moreover, the effects of βME and ethanol on E33C/Y418C-L1 adhesion were non-additive. The cutoff for alcohol inhibition of WT-L1 adhesion was between 1-butanol and 1-pentanol. Increasing the size of the alcohol binding pocket by mutating Glu-33 to Ala-33, increased the alcohol cutoff from 1-butanol to 1-decanol. These findings support the hypothesis that alcohol binding within a pocket bordered by Glu-33 and Tyr-418 inhibits L1 adhesion by disrupting the Ig1-Ig4 interaction.


48) MATERNAL HEALTH BEHAVIOURS DURING PREGNANCY IN AN IRISH OBSTETRIC POPULATION AND THEIR ASSOCIATIONS WITH SOCIO-DEMOGRAPHIC AND INFANT CHARACTERISTICS
Tarrant RC, Younger KM, Sheridan-Pereira M, Kearney JM.
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ABSTRACT
Background/Objectives: To examine the prevalence and combined occurrence of peri-conceptional
folic acid (FA) supplement use, smoking and alcohol consumption during pregnancy in a sample of women in Dublin, and determine the factors associated with these health behaviours.

Subjects/Methods:A prospective observational study (2004-2006) involving the recruitment of 491 pregnant women from antenatal clinics in a Dublin maternity hospital, with postpartum follow-up of 450 eligible mothers. Data on FA use, maternal smoking and alcohol consumption patterns during pregnancy were collected from the antenatal patient-administered questionnaire, which was completed by participants, and returned to the investigator on the day of recruitment.

Results: The median gestational age of women at recruitment was 36 weeks. A combined 24.2% of mothers commenced FA at the recommended time, avoided alcohol consumption and smoking during pregnancy. In all, 35.3% of mothers reported to consuming alcohol, 20.9% smoked during pregnancy and 44.4% commenced FA at the recommended time. Mothers <25 years were more likely to have not taken FA at the recommended time (adjusted odds ratio (aOR): 4.0, 95% confidence interval (CI): 1.64-9.77) and were more likely to have smoked during pregnancy (aOR: 3.56, 95% CI: 1.32-9.57). Irish nationality positively predicted both alcohol consumption (aOR: 4.37, 95% CI: 1.88-10.15) and smoking (aOR: 10.92, 95% CI: 1.35-87.98) during pregnancy.

Conclusions: Educational efforts are still necessary to convince women of Irish nationality, in particular, of the adverse effects of smoking and alcohol consumption on fetal outcome. Women <25 years should be specifically targeted in smoking cessation and FA promotional campaigns.


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Unbound Medicine, Brain Behav Immun 2011 Mar 2.

49) PROTECTION OF NEURONS AND MICROGlia AGAINST ETHANOL IN A MOUSE MODEL OF FETAL ALCOHOL SPECTRUM DISORDERS BY PEROxisome PROLIFERATOR ACTIVATED RECEPTOR-γ AGONISTS
Kane CJ, Phelan KD, Han L, Smith RR, Xie J, Douglas JC, Drew PD

ABSTRACT
Fetal alcohol spectrum disorders (FASD) result from ethanol exposure to the developing fetus and are the most common cause of mental retardation in the United States. These disorders are characterized by a variety of neurodevelopmental and neurodegenerative anomalies which result in significant lifetime disabilities. Thus, novel therapies are required to limit the devastating consequences of FASD. Neuropathology associated with FASD can occur throughout the central nervous system (CNS), but is particularly well characterized in the developing cerebellum. Rodent models of FASD have previously demonstrated that both Purkinje cells and granule cells, which are the two major types of neurons in the cerebellum, are highly susceptible to the toxic effects of ethanol. The current studies demonstrate that ethanol decreases the viability of cultured cerebellar granule cells and microglial cells. Interestingly, microglia have dual functionality in the CNS. They provide trophic and protective support to neurons. However, they may also become pathologically activated and produce inflammatory molecules toxic to parenchymal cells including neurons. The findings in this study demonstrate that the peroxisome proliferator-activated receptor-gamma agonists 15-deoxy- Δ12,15 prostaglandin J2 and pioglitazone protect cultured granule cells and microglia from the toxic effects of ethanol. Furthermore, investigations using a newly developed mouse model of FASD and stereological cell counting methods in the cerebellum elucidate that ethanol administration to neonates is toxic to both Purkinje cell neurons as well as microglia, and that in vivo administration of PPAR-gamma agonists
protects these cells. In composite, these studies suggest that PPAR-gamma agonists may be effective in limiting ethanol-induced toxicity to the developing CNS.

**Link to the Article,**
[http://www.unboundmedicine.com/medline/ebm/record/21376806/abstract/Protection_of_Neurons_and_Microglia_Against_Ethanol_in_a_Mouse_Model_of_Fetal_Alcohol_Spectrum_Disorders_by_Peroxisome_Proliferator_Activated_Receptor_y_Agonists](http://www.unboundmedicine.com/medline/ebm/record/21376806/abstract/Protection_of_Neurons_and_Microglia_Against_Ethanol_in_a_Mouse_Model_of_Fetal_Alcohol_Spectrum_Disorders_by_Peroxisome_Proliferator_Activated_Receptor_y_Agonists)

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50) **THE SPECTRUM OF HEMISPHERAL CORTEX LESIONS IN INTRAUTERINE ALCOHOLIC INTOXICATION**

Chikhladze R, Ramishvili N, Tsagareli Z, Kikalishvili N.
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**ABSTRACT**

Aim of the study was to examine the specific morphological changes of brain cortex in fetal alcoholic intoxication model. The latter was performed in male and female animals by substituting water with 15% ethyl alcohol during 1 month period, which was followed by putting pregnant females on alcohol of the same concentration for the duration of the whole period of pregnancy (21 days). 24 experimental and 10 control (intact) animals were subjected to study overall. The study material applied the samples of brain convexital cortex from foetus and newborn rats. Paraffin-embedded slices (films) were dyed by the method of Nissle and hematoxylin eosin. After immersion fixation in 2.5% glutaraldehyde and 1% osmium acid solutions followed by double contrasting, the ultrathin slices were studied in the electron microscope Tesla BS 500. Macroscopic study demonstrated the hyperemia of pia with partial incorporation, different types of neuroorganogenesis disturbance, also, leptomeningal heterotopia and microcephaly in 6 cases from 24 (25%) in the experimental group. Morphology of cortical damage to fetal brain in alcoholic intoxication was demonstrated by progressive massive destruction of neuronal mitochondria, involutional changes in dendrites and their processes and glial proliferation, which possibly account for the structural basis of energetic and informational deficit in neurons. Acquired data may be extrapolated on human model of alcoholic embryopathy with subsequent cognitive problems.

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51) **THE EFFECTS OF ALCOHOL ON FETAL DEVELOPMENT**

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**ABSTRACT**

Prenatal exposure to alcohol has profound effects on many aspects of fetal development. Although alterations of somatic growth and specific minor malformations of facial structure are most
characteristic, the effects of alcohol on brain development are most significant in that they lead to substantial problems with neurobehavioral development. Since the initial recognition of the fetal alcohol syndrome (FAS), a number of important observations have been made from studies involving both humans and animals. Of particular importance, a number of maternal risk factors have been identified, which may well be of relevance relative to the development of strategies for prevention of the FAS as well as intervention for those who have been affected. These include maternal age >30 years, ethnic group, lower socioeconomic status, having had a previously affected child, maternal under-nutrition, and genetic background. The purpose of this review is to discuss these issues as well as to set forth a number of questions that have not adequately been addressed relative to alcohol's effect on fetal development. Of particular importance is the critical need to identify the full spectrum of structural defects associated with the prenatal effects of alcohol as well as to establish a neurobehavioral phenotype. Appreciation of both of these issues is necessary to understand the full impact of alcohol on fetal development.

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52) RE-AIM EVALUATION OF THE ALCOHOL AND PREGNANCY PROJECT: EDUCATIONAL RESOURCES TO INFORM HEALTH PROFESSIONALS ABOUT PRENATAL ALCOHOL EXPOSURE AND FETAL ALCOHOL SPECTRUM DISORDER
Payne JM, France KE, Henley N, D’Antoine HA, Bartu AE, O’Leary CM, Elliott EJ, Bower C, Geelhoed E.
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ABSTRACT
The objective was to evaluate the Alcohol and Pregnancy Project that provided health professionals in Western Australia (WA) with educational resources to inform them about prevention of prenatal alcohol exposure and fetal alcohol spectrum disorder (FASD). The authors developed, produced, and distributed educational resources to 3,348 health professionals in WA. Six months later, they surveyed 1,483 of these health professionals. The authors used the RE-AIM framework (reach, effectiveness, adoption, implementation, and maintenance) to evaluate the project. The educational resources were effective in producing a 31% increase in the proportion of health professionals who routinely provided pregnant women with information about the consequences of drinking alcohol during pregnancy. One hundred percent of the settings adopted the project, it reached 96.3% of the target population, it was implemented as intended, and the resources were maintained (http://www.ichr.uwa.edu.au/alcoholandpregnancy). The educational resources for health professionals have potential to contribute to reducing prenatal alcohol exposure and FASD.

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53) VENTROMEDIAN FOREBRAIN DYSGENESIS FOLLOWS EARLY PRENATAL ETHANOL EXPOSURE IN MICE
Godin EA, Dehart DB, Parnell SE, O'Leary-Moore SK, Sulik KK.

ABSTRACT
Ethanol exposure on gestational day (GD) 7 in the mouse has previously been shown to result in ventromedian forebrain deficits along with facial anomalies characteristic of fetal alcohol syndrome (FAS). To further explore ethanol's teratogenic effect on the ventromedian forebrain in this mouse model, scanning electron microscopic and histological analyses were conducted. For this, time mated C57Bl/6J mice were injected with 2.9g/kg ethanol or saline twice, at a 4h interval, on their 7th day of pregnancy. On GD 12.5, 13 and 17, control and ethanol-exposed specimens were collected and processed for light and scanning electron microscopic analyses. Gross morphological changes present in the forebrains of ethanol-exposed embryos included cerebral hemispheres that were too close in proximity or rostrally united, enlarged foramina of Monro, enlarged or united lateral ventricles, and varying degrees of hippocampal and ventromedian forebrain deficiency. In GD 12.5 control and ethanol-exposed embryos, in situ hybridization employing probes for Nkx2.1 or Fzd8 to distinguish the preoptic area and medial ganglionic eminences (MGEs) from the lateral ganglionic eminences, respectively, confirmed the selective loss of ventromedian tissues. Immunohistochemical labeling of oligodendrocyte progenitors with Olig2, a transcription factor necessary for their specification, and of GABA, an inhibitory neurotransmitter, showed ethanol-induced reductions in both. To investigate later consequences of ventromedian forebrain loss, MGE-derived somatostatin-expressing interneurons in the subpallial region of GD 17 fetal mice were examined, with results showing that the somatostatin-expressing interneurons that were present were dysmorphic in the ethanol-exposed fetuses. The potential functional consequences of this insult are discussed.

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54) NEUROPSYCHOLOGICAL COMPARISON OF CHILDREN WITH HEAVY PRENATAL ALCOHOL EXPOSURE AND AN IQ-MATCHED COMPARISON GROUP
Vaurio L, Riley EP, Mattson SN.
Department of Psychology, Center for Behavioral Teratology, San Diego State University, San Diego, California.

ABSTRACT
An objective in current research on children with fetal alcohol spectrum disorders (FASD) is to determine neurobehavioral profiles to identify affected individuals. Deficits observed when children with FASD are compared to typically developing controls may be confounded by lower IQ scores in the subjects with FASD. To determine if prenatal alcohol exposure is associated with neurobehavioral deficits after controlling for IQ differences, multivariate analyses were conducted to compare alcohol-exposed (ALC) subjects to a comparison group closely matched on IQ (IQC). The initial analysis included a broad neuropsychological battery with measures of language, executive function, visual-motor integration, motor ability, and academic achievement. Additional, in depth comparisons focused on visual sustained attention, verbal learning and memory and parent/guardian-reported behavior problems. Group differences (ALC < IQC) were found on verbal learning and parent-rated behavior problems. Group differences were marginally significant (measures within the broad
neuropsychological comparison) or not significant (visual attention, retention of verbal material) on the remaining comparisons. Therefore, some deficits (e.g., verbal learning and behavior problems) in children with heavy prenatal alcohol exposure cannot be explained by the lower FSIQ observed in the population. These areas of relative weakness could be useful in distinguishing children with FASD from other children with lowered IQ. (JINS, 2011, 17, 1-11).

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55) WHAT DOES DIFFUSION TENSOR IMAGING REVEAL ABOUT THE BRAIN AND COGNITION IN FETAL ALCOHOL SPECTRUM DISORDERS?
Wozniak JR, Muetzel RL.
Department of Psychiatry, University of Minnesota Twin Cities, F256/2B West, 2450 Riverside Ave., Minneapolis, MN, 55454, USA, jwozniak@umn.edu.

ABSTRACT
Over the past 5 years, Diffusion Tensor Imaging (DTI) has begun to provide new evidence about the effects of prenatal alcohol exposure on white matter development. DTI, which examines microstructural tissue integrity, is sensitive to more subtle white matter abnormalities than traditional volumetric MRI methods. Thus far, the available DTI data suggest that white matter microstructural abnormalities fall on a continuum of severity in Fetal Alcohol Spectrum Disorder (FASD). Abnormalities are prominent in the corpus callosum, but also evident in major anterior-posterior fiber bundles, corticospinal tracts, and cerebellum. These subtle abnormalities are correlated with neurocognitive deficits, especially in processing speed, non-verbal ability, and executive functioning. Future studies using larger samples, increasingly sophisticated DTI methods, and additional functional MRI connectivity measures will better characterize the full range of abnormalities in FASD. Ultimately, these measures may serve as indices of change in future longitudinal studies and in studies of interventions for FASD.

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56) ETHANOL INFLUENCES ON BAX TRANSLOCATION, MITOCHONDRIAL MEMBRANE POTENTIAL, AND REACTIVE OXYGEN SPECIES GENERATION ARE MODULATED BY VITAMIN E AND BRAIN- DERIVED NEUROTROPHIC FACTOR
Heaton MB, Paiva M, Siler-Marsiglio K.
From the Department of Neuroscience, University of Florida College of Medicine, McKnight Brain Institute, Center for Alcohol Research, Gainesville, Florida.

ABSTRACT
Background: This study investigated ethanol influences on intracellular events that predispose developing neurons toward apoptosis and the capacity of the antioxidant α-tocopherol (vitamin E) and the neurotrophin brain-derived neurotrophic factor (BDNF) to modulate these effects. Assessments
were made of the following: (i) ethanol-induced translocation of the pro-apoptotic Bax protein to the mitochondrial membrane, a key upstream event in the initiation of apoptotic cell death; (ii) disruption of the mitochondrial membrane potential (MMP) as a result of ethanol exposure, an important process in triggering the apoptotic cascade; and (iii) generation of damaging reactive oxygen species (ROS) as a function of ethanol exposure.

Methods: These interactions were investigated in cultured postnatal day 8 neonatal rat cerebellar granule cells, a population vulnerable to developmental ethanol exposure in vivo and in vitro. Bax mitochondrial translocation was analyzed via subcellular fractionation followed by Western blot, and mitochondrial membrane integrity was determined using the lipophilic dye, JC-1, that exhibits potential-dependent accumulation in the mitochondrial membrane as a function of the MMP.

Results: Brief ethanol exposure in these preparations precipitated Bax translocation, but both vitamin E and BDNF reduced this effect to control levels. Ethanol treatment also resulted in a disturbance of the MMP, and this effect was blunted by the antioxidant and the neurotrophin. ROS generation was enhanced by a short ethanol exposure in these cells, but the production of these harmful free radicals was diminished to control levels by cotreatment with either vitamin E or BDNF.

Conclusions: These results indicate that both antioxidants and neurotrophic factors have the potential to ameliorate ethanol neurotoxicity and suggest possible interventions that could be implemented in preventing or lessening the severity of the damaging effects of ethanol in the developing central nervous system seen in the fetal alcohol syndrome (FAS).


57) CHRONIC ETHANOL EXPOSURE AND FOLIC ACID SUPPLEMENTATION: FETAL GROWTH AND FOLATE STATUS IN THE MATERNAL AND FETAL GUINEA PIG
Hewitt AJ, Knuff AL, Jefkins MJ, Collier CP, Reynolds JN, Brien JF.
Department of Pharmacology and Toxicology, Queen's University, Kingston, ON, Canada.

ABSTRACT
Chronic ethanol exposure (CEE) can produce developmental abnormalities in the CNS of the embryo and developing fetus. Folic acid (FA) is an important nutrient during pregnancy and low folate status exacerbates ethanol-induced teratogenicity. This study tested the hypotheses that (1) CEE depletes folate stores in the mother and fetus; and (2) maternal FA supplementation maintains folate stores. CEE decreased fetal body, brain, hippocampus weights, and brain to body weight ratio but not hippocampus to body weight ratio. These effects of CEE were not mitigated by maternal FA administration. The FA regimen prevented the CEE-induced decrease of term fetal liver folate. However, it did not affect maternal liver folate or fetal RBC folate at term, and did not mitigate the nutritional deficit-induced decrease of term fetal hippocampus folate. This study suggests that maternal FA supplementation may have differential effects on folate status in the mother and the fetus.


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ABSTRACT
Background: Maternal alcohol abuse during pregnancy can lead to fetal neurotoxicity and fetal alcohol spectrum disorder (FASD).

Aims: To compare the clinical features and neurobehavioral profiles of children exposed to alcohol during pregnancy with controls.

Methodology: Children exposed to alcohol in utero (n = 26) and 27-years age- and sex-matched controls were compared on FAS facial features, minor physical anomalies (MPAs), anthropometric measures, behavioral problems and intellectual functioning.

Results: MPAs were more common in cases (p = 0.001). Among FAS facial features, only philtrum smoothness varied significantly between the groups (p = 0.001). Behavioral problems (on Childhood Behavior Check List) were more pronounced (p = 0.001) and intellectual functioning significantly poorer in cases (p = 0.001) compared to controls.

Conclusions: Children prenatally exposed to alcohol manifest several neurobehavioral problems compared to controls. Underlying malnutrition may have altered some of the clinical findings.


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importantly, combined treatment with subthreshold levels of agrin MO and ethanol produces pronounced microphthalmia, markedly reduces agrin gene expression, and perturbs Pax6a and Mbx gene expression. Microphthalmia produced by combined agrin MO and ethanol treatment was rescued by sonic hedgehog (Shh) mRNA overexpression, suggesting that ethanol-mediated disruption of agrin expression results in disrupted Shh function.

**Conclusions:** These studies illustrate the strong potential for using zebrafish as a model to aid in defining the molecular basis for ethanol's teratogenic effects. The results of this work suggest that agrin expression and function may be a target of ethanol exposure during embryogenesis.


60) A DROSOPHILA MODEL FOR FETAL ALCOHOL SYNDROME DISORDERS: ROLE FOR THE INSULIN PATHWAY
McClure KD, French RL, Heberlein U.
Department of Anatomy, University of California, San Francisco, San Francisco, CA 94143, USA.

**ABSTRACT**
Prenatal exposure to ethanol in humans results in a wide range of developmental abnormalities, including growth deficiency, developmental delay, reduced brain size, permanent neurobehavioral abnormalities and fetal death. Here we describe the use of Drosophila melanogaster as a model for exploring the effects of ethanol exposure on development and behavior. We show that developmental ethanol exposure causes reduced viability, developmental delay and reduced adult body size. We find that flies reared on ethanol-containing food have smaller brains and imaginal discs, which is due to reduced cell division rather than increased apoptosis. Additionally, we show that, as in mammals, flies reared on ethanol have altered responses to ethanol vapor exposure as adults, including increased locomotor activation, resistance to the sedating effects of the drug and reduced tolerance development upon repeated ethanol exposure. We have found that the developmental and behavioral defects are largely due to the effects of ethanol on insulin signaling; specifically, a reduction in Drosophila insulin-like peptide (Dilp) and insulin receptor expression. Transgenic expression of Dilp proteins in the larval brain suppressed both the developmental and behavioral abnormalities displayed by ethanol-reared adult flies. Our results thus establish Drosophila as a useful model system to uncover the complex etiology of fetal alcohol syndrome.

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61) INTER-HEMISPHERIC FUNCTIONAL CONNECTIVITY DISRUPTION IN CHILDREN WITH PRENATAL ALCOHOL EXPOSURE
Wozniak JR, Mueller BA, Muetzel RL, Bell CJ, Hoecker HL, Nelson ML, Chang PN, Lim KO.
From the Department of Psychiatry, University of Minnesota, Minneapolis, MN.

**ABSTRACT**
**Background:** MRI studies, including recent diffusion tensor imaging (DTI) studies, have shown
corpus callosum abnormalities in children prenatally exposed to alcohol, especially in the posterior regions. These abnormalities appear across the range of fetal alcohol spectrum disorders (FASD). Several studies have demonstrated cognitive correlates of callosal abnormalities in FASD including deficits in visual-motor skill, verbal learning, and executive functioning. The goal of this study was to determine whether inter-hemispheric structural connectivity abnormalities in FASD are associated with disrupted inter-hemispheric functional connectivity and disrupted cognition.

**Methods:** Twenty-one children with FASD and 23 matched controls underwent a 6-minute resting-state functional MRI scan as well as anatomical imaging and DTI. Using a semi-automated method, we parsed the corpus callosum and delineated 7 inter-hemispheric white matter tracts with DTI tractography. Cortical regions of interest (ROIs) at the distal ends of these tracts were identified. Right-left correlations in resting fMRI signal were computed for these sets of ROIs, and group comparisons were made. Correlations with facial dysmorphology, cognition, and DTI measures were computed.

**Results:** A significant group difference in inter-hemispheric functional connectivity was seen in a posterior set of ROIs, the para-central region. Children with FASD had functional connectivity that was 12% lower than in controls in this region. Subgroup analyses were not possible owing to small sample size, but the data suggest that there were effects across the FASD spectrum. No significant association with facial dysmorphology was found. Para-central functional connectivity was significantly correlated with DTI mean diffusivity, a measure of microstructural integrity, in posterior callosal tracts in controls but not in FASD. Significant correlations were seen between these structural and functional measures, and Wechsler perceptual reasoning ability.

**Conclusions:** Inter-hemispheric functional connectivity disturbances were observed in children with FASD relative to controls. The disruption was measured in medial parietal regions (para-central) that are connected by posterior callosal fiber projections. We have previously shown microstructural abnormalities in these same posterior callosal regions, and the current study suggests a possible relationship between the two. These measures have clinical relevance as they are associated with cognitive functioning.

Read Full Article,  

Received: 25 August 2010; Accepted: 8 February 2011; Published: 8 February 2011

62) UNDER-REPORTING OF FOETAL ALCOHOL SPECTRUM DISORDERS: AN ANALYSIS OF HOSPITAL EPISODE STATISTICS
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⁴ FASD Specialist Behavioural Clinic, Surrey and Border Partnership NHS Foundation Trust, 116-118 Station Road East, Oxted, Surrey, RH8 0QA UK

**ABSTRACT**
**Background:** Internationally, 0.97 per 1,000 live births are affected by foetal alcohol syndrome (FAS).
However, prevalence intelligence has been limited in the UK, hindering the development of appropriate services. This analysis compares hospital admissions over time, between regions and with alcohol-related admissions for adult females to assess whether established patterns (such as the North experiencing elevated harms) can be identified.

Methods: A retrospective analysis of hospital admissions data (April 2002 to March 2008) for foetal alcohol spectrum disorder (FASD)-related conditions: foetal alcohol syndrome (dysmorphic) (n=457); foetus and newborn affected by maternal use of alcohol (n=157); maternal care for (suspected) damage to foetus from alcohol (n=285); and 322,161 women admitted due to alcohol-related conditions.

Results: Whilst the rate of admission for alcohol-related conditions in women aged 15-44 years increased significantly by 41% between 2002/03 and 2007/08 (p<0.0001), no such increases were seen in the numbers of FASD-related conditions (all p<0.05). Established regional rates of admission for alcohol-related conditions in women aged 15-44 years old were not associated with admission for FASD-related conditions.

Conclusions: It would be expected that the North West and North East regions, known to have higher levels of alcohol harm would have higher levels of FASD-related conditions. However, this was not reflected in the incidence of such conditions, suggesting under-reporting. With incomplete datasets, intelligence systems are severely limited, hampering efforts to develop targeted interventions. Improvements to intelligence systems, practitioner awareness and screening are essential in tackling this.

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63) MODERATE PRENATAL ALCOHOL EXPOSURE AND SEROTONIN GENOTYPE INTERACT TO ALTER CNS SEROTONIN FUNCTION IN RHESUS MONKEY OFFSPRING

Schneider ML, Moore CF, Barr CS, Larson JA, Kraemer GW.

From the Department of Kinesiology (MLS, JAL), University of Wisconsin-Madison, Madison, Wisconsin; Department of Psychology (CFM), University of Wisconsin-Madison, Madison, Wisconsin; Harlow Center for Biological Psychology (MLS, JAL), University of Wisconsin-Madison, Madison, Wisconsin; National Institute on Alcohol Abuse and Alcoholism (NIAAA) (CSB), National Institute of Health, Maryland; and Department of Psychology (GWK), University of Toronto, Toronto, Ontario, Canada.

ABSTRACT

Background: Moderate prenatal alcohol exposure can contribute to neurodevelopmental impairments and disrupt several neurotransmitter systems. We examined the timing of moderate level alcohol exposure, serotonin transporter gene polymorphic region variation (rh5-HTTLPR), and levels of primary serotonin and dopamine (DA) metabolites in cerebrospinal fluid (CSF) in rhesus monkeys.

Methods: Thirty-two 30-month old rhesus monkeys (Macaca mulatta) from 4 groups of females were assessed: (i) early alcohol-exposed group (n = 9), in which mothers voluntarily consumed 0.6 g/kg/d alcohol solution on gestational days 0 to 50; (ii) middle-to-late gestation alcohol-exposed group (n = 6), mothers consumed 0.6 g/kg/d alcohol solution on gestational days 50 to 135; (iii) a continuous-exposure group (n = 8), mothers consumed 0.6 g/kg/d alcohol solution on gestational days 0 to 135; and (iv) controls (n = 9), mothers consumed an isocaloric control solution on...
gestational days 0 to 50, 50 to 135, or 0 to 135. Serotonin transporter promoter region allelic variants (homozygous s/s or heterozygous s/l vs. homozygous l/l) were determined. We examined CSF concentrations of the 5-HT and DA metabolites, 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA), respectively, at baseline and 50 hours after separation from cage-mates, when the monkeys were 30 months old.

**Results:** Early- and middle-to-late gestation-alcohol exposed monkeys carrying the short allele had lower concentrations of 5-HIAA in CSF relative to other groups. Concentrations of 5-HIAA in CSF were lower for s allele carriers and increased from baseline relative to pre-separation values, whereas 5-HIAA levels in l/l allele carriers were not affected by separation. Monkeys carrying the short allele had lower basal concentrations of HVA in CSF compared with monkeys homozygous for the long allele.

**Conclusion:** Carrying the s allele of the 5-HT transporter increased the probability of reduced 5-HIAA in early- and middle-to-late gestation alcohol-exposed monkeys and reduced HVA at baseline. These findings that prenatal alcohol exposure altered central 5-HT activity in genetically sensitive monkeys raise questions about whether abnormal serotonin biological pathways could underlie some of the psychiatric disorders reported in fetal alcohol spectrum disorder.


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64) **THE PROCESS AND BENEFITS OF A UNIVERSITY AND STATE HEALTH AGENCY COLLABORATION FOR ALCOHOL-FREE PREGNANCIES IN OREGON**

Jessica W Henderson, Lesa Dixon-Gray

**ABSTRACT**

**Background:** A significant number of college women are at risk for alcohol-exposed pregnancies because the ages of the heaviest alcohol consumption is typically 18 through 21 years, and contraception may be used ineffectively or not at all. These risks call for greater prevention efforts.

**Objective:** Collaboration between a higher education institution and a government health agency to reduce alcohol-exposed pregnancies in Oregon.

**Methods:** Health professionals from the Fetal Alcohol Syndrome (FAS) Prevention Program of the Oregon Public Health Division presented current research and explained the mission of a Center for Disease Control (CDC) cooperative agreement to university students in a Health Communication course. The students then developed social marketing messages that targeted alcohol use and/or contraception behavior.

**Results:** At the end of the course, the students presented their campaigns campus-wide, and to the state agency. Four of the theory-based messages are illustrated in this article.

**Conclusion:** The students brought to the state FAS Program a specific range of knowledge, vocabulary and creative skills to create messages for young adults. University students reported benefits of becoming familiar with government agencies and working on “real-life” projects that had the
potential to be used in community settings.

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65) CO-REGULATION OF MOVEMENT SPEED AND ACCURACY BY CHILDREN WITH HEAVY PRENATAL ALCOHOL EXPOSURE
Simmons RW, Madra NJ, Levy SS, Riley EP, Mattson SN.
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ABSTRACT
The study investigated how children with heavy prenatal alcohol exposure regulate movement speed and accuracy during goal-directed movements. 16 children ages 7 to 17 years with confirmed histories of heavy in utero alcohol exposure, and 21 nonalcohol-exposed control children completed a series of reciprocal tapping movements between two spatial targets. 5 different targets sets were presented, representing a range of task difficulty between 2 and 6 bits of information. Estimates of percent error rate, movement time, slope, and linear fit of the resulting curve confirmed that for goal-directed, reciprocal tapping responses, performance of the group with prenatal alcohol exposure was described by a linear function, as predicted by Fitts' law, by sacrificing movement accuracy. The index of performance was the same for the two groups: it initially increased, then leveled off for more difficult movements.


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66) PRENATAL EXPOSURE TO TOBACCO AND ALCOHOL ARE ASSOCIATED WITH CHRONIC DAILY HEADACHES AT CHILDHOOD: A POPULATION-BASED STUDY
Arruda MA, Guidetti V, Galli F, Albuquerque RC, Bigal ME.
Glia Institute, Ribeirão Preto, SP, Brazil. arruda@institutoglia.com.br

ABSTRACT
The influence of prenatal events on the development of headaches at childhood has not been investigated and is the scope of our study. Of 2,173 children identified as the target sample, consents and analyzable data were provided by 1,440 (77%). Parents responded to a standardized questionnaire with a validated headache module and specific questions about prenatal exposures. Odds of chronic daily headache (CDH) were significantly higher when maternal tabagism was reported. When active and passive smoking were reported, odds ratio (OR) of CDH were 2.29 [95% confidence intervals (CI)=1.6 vs. 3.6]); for active tabagism, OR=4.2 (95% CI=2.1-8.5). Alcohol use more than doubled the chance of CDH (24% vs. 11%, OR=2.3, 95% CI=1.2-4.7).

In multivariate analyses, adjustments did not substantially change the smoking/CDH association.

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Prenatal exposure to tobacco and alcohol are associated with increased rates of CDH onset in preadolescent children.

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67) FETAL EXPOSURE TO ALCOHOL, DEVELOPMENTAL BRAIN ANOMALY, AND VITAMIN A DEFICIENCY: A CASE REPORT
Goez HR, Scott O, Hasal S.
Division of Pediatric Neurology, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada. helly.goez@albertahealthservices.ca

ABSTRACT
Prenatal alcohol exposure is a cause of congenital brain malformations such as hydrocephalus; however, a complete mechanism accounting for this phenomenon has yet to be discovered. We report a case of a newborn who was exposed to alcohol throughout pregnancy and presented with low serum vitamin A and hydrocephalus. To our knowledge, the connection between prenatal ethanol exposure, vitamin A deficiency, and a developmental brain anomaly has never been described in humans before. A possible mechanism may be mediated by disruption of the homeostasis of vitamin A, an important morphogen in the developing nervous system. This, in turn, compromises the activity of the floor plate, a structure in charge of polarization and midline formation in the neural tube. We conclude that vitamin A screening and supplementation might be recommended for newborns of mothers who ingested ethanol during pregnancy.

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68) ALCOHOL CONSUMPTION DURING PREGNANCY: PREVALENCE AND PROVIDER ASSESSMENT
Cheng D, Kettinger L, Uduhiri K, Hurt L.
Center for Maternal and Child Health, Maryland Department of Health and Mental Hygiene, Baltimore, MD 21201, USA. chengd@dhmh.state.md.us

ABSTRACT
Objective: To estimate the prevalence of prenatal alcohol consumption and the extent of provider screening and discussion about alcohol use during pregnancy.

Methods: Data were obtained from a stratified random sample of 12,611 mothers from Maryland who delivered live infants during the years 2001-2008 and completed the Maryland Pregnancy Risk Assessment Monitoring System survey. Analyses were conducted using Proc Surveyfreq in SAS 9.2.

Results: Nearly 8% (95% confidence interval 7.1-8.4) of mothers from Maryland reported alcohol consumption during the last 3 months of pregnancy. The highest prevalence of late-pregnancy alcohol
consumption was reported by mothers who were non-Hispanic white, (10.9%, confidence interval 9.8-11.9), aged 35 years or older (13.4%, confidence interval 12.4-14.4), and college graduates (11.4%, confidence interval 10.2-12.6) (P<.001). Nineteen percent (confidence interval 17.6-21.0) of mothers reported that their prenatal care provider did not ask whether they were drinking alcoholic beverages, and 30% (confidence interval 28.3-30.8) reported that a healthcare provider did not counsel them about the consequences of alcohol use on the child. Reported screening and counseling were least prevalent among mothers who were non-Hispanic white, aged 35 years or older, and college graduates (P<.01).

**Conclusion:** Despite the substantial number of women who continue to drink alcohol during pregnancy, healthcare providers do not routinely assess alcohol consumption or counsel all women about its harmful effects. Counseling was least prevalent among the same groups of women with the highest rates for drinking. Provider alcohol assessment, as recommended by the U.S. Surgeon General to prevent alcohol misuse, needs further promotion as a routine part of prenatal care.

**Level of Evidence:** II

**Link to the Article,**


69) **IMPAIRED DELAY AND TRACE EYEBLINK CONDITIONING IN SCHOOL-AGE CHILDREN WITH FETAL ALCOHOL SYNDROME**

Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, Michigan 48207, USA. sandra.jacobson@wayne.edu

**ABSTRACT**

**Background:** Classical eyeblink conditioning (EBC) involves contingent temporal pairing of a conditioned stimulus (e.g., tone) with an unconditioned stimulus (e.g., air puff). Impairment of EBC has been demonstrated in studies of alcohol-exposed animals and in children exposed prenatally at heavy levels.

**Methods:** Fetal alcohol syndrome (FAS) was diagnosed by expert dysmorphologists in a large sample of Cape Coloured, South African children. Delay EBC was examined in a new sample of 63 children at 11.3 years, and trace conditioning in 32 of the same children at 12.8 years. At each age, 2 sessions of 50 trials each were administered on the same day; 2 more sessions the next day, for children not meeting criterion for conditioning.

**Results:** Six of 34 (17.6%) children born to heavy drinkers were diagnosed with FAS, 28 were heavily exposed nonsyndromal (HE), and 29 were nonexposed controls. Only 33.3% with FAS and 42.9% of HE met criterion for delay conditioning, compared with 79.3% of controls. The more difficult trace conditioning task was also highly sensitive to fetal alcohol exposure. Only 16.7% of the FAS and 21.4% of HE met criterion for trace conditioning, compared with 66.7% of controls. The magnitude of the effect of diagnostic group on trace conditioning was not greater than the effect on short delay conditioning, findings consistent with recent rat studies. Longer latency to onset and peak eyeblink CR in exposed children indicated poor timing and failure to blink in anticipation of the puff. Extended
training resulted in some but not all of the children reaching criterion.

**Conclusions:** These data showing alcohol-related delay and trace conditioning deficits extend our earlier findings of impaired EBC in 5-year-olds to school-age. Alcohol-related impairment in the cerebellar circuitry required for both forms of conditioning may be sufficient to account for the deficit in both tasks. Extended training was beneficial for some exposed children. EBC provides a well-characterized model system for assessment of degree of cerebellar-related learning and memory dysfunction in fetal alcohol exposed children.

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70) **ADMINISTRATION OF MEMANTINE DURING ETHANOL WITHDRAWAL IN NEONATAL RATS: EFFECTS ON LONG-TERM ETHANOL-INDUCED MOTOR INCOORDINATION AND CEREBELLAR PURKINJE CELL LOSS**

Idrus NM, McGough NN, Riley EP, Thomas JD.  
Department of Psychology, Center for Behavioral Teratology, San Diego State University, California 92120, USA.

**ABSTRACT**  
**Background:** Alcohol consumption during pregnancy can damage the developing fetus, illustrated by central nervous system dysfunction and deficits in motor and cognitive abilities. Binge drinking has been associated with an increased risk of fetal alcohol spectrum disorders, likely due to increased episodes of ethanol withdrawal. We hypothesized that overactivity of the N-methyl-D-aspartate (NMDA) receptor during ethanol withdrawal leads to excitotoxic cell death in the developing brain. Consistent with this, administration of NMDA receptor antagonists (e.g., MK-801) during withdrawal can attenuate ethanol's teratogenic effects.

The aim of this study was to determine whether administration of memantine, an NMDA receptor antagonist, during ethanol withdrawal could effectively attenuate ethanol-related deficits, without the adverse side effects associated with other NMDA receptor antagonists.

**Methods:** Sprague-Dawley pups were exposed to 6.0 g/kg ethanol or isocaloric maltose solution via intubation on postnatal day 6, a period of brain development equivalent to a portion of the 3rd trimester. Twenty-four and 36 hours after ethanol, subjects were injected with 0, 10, or 15 mg/kg memantine, totaling doses of 0, 20, or 30 mg/kg. Motor coordination was tested on a parallel bar task and the total number of cerebellar Purkinje cells was estimated using unbiased stereology.

**Results:** Alcohol exposure induced significant parallel bar motor incoordination and reduced Purkinje cell number. Memantine administration significantly attenuated both ethanol-associated motor deficits and cerebellar cell loss in a dose-dependent manner.

**Conclusions:** Memantine was neuroprotective when administered during ethanol withdrawal. These
data provide further support that ethanol withdrawal contributes to fetal alcohol spectrum disorders.

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71) MEMORY AND BRAIN VOLUME IN ADULTS PRENATALLY EXPOSED TO ALCOHOL
Coles CD, Goldstein FC, Lynch ME, Chen X, Kable JA, Johnson KC, Hu X.
Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA 30322, United States. ccoles@emory.edu

ABSTRACT
The impact of prenatal alcohol exposure on memory and brain development was investigated in 92 African-American, young adults who were first identified in the prenatal period. Three groups (Control, n=26; Alcohol-related Neurodevelopmental Disorder, n=36; and Dysmorphic, n=30) were imaged using structural MRI with brain volume calculated for multiple regions of interest. Memory was measured using the Verbal Selective Reminding Memory Test and its nonverbal counterpart, the Nonverbal Selective Reminding Memory Test, which each yielding measures of learning and recall. For both Verbal and Nonverbal Recall and Slope, linear trends were observed demonstrating a spectrum of deficits associated with prenatal alcohol exposure. Dysmorphic individuals performed significantly poorer than unexposed controls on 5 of 6 memory outcomes. Alcohol-exposed individuals demonstrated significantly lower total brain volume than controls, as well as lower volume in a number of specific regions including hippocampus. Mediation analyses indicated that memory performance associated with effects of prenatal alcohol exposure was mediated from dysmorphic severity through hippocampal volume, particularly right hippocampus. These results indicate that the association between the physical effects of prenatal alcohol exposure and deficits in memory are mediated by volumetric reduction in specific brain regions.

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72) REINFORCEMENT LEARNING IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER
Jennifer A Engle, Kimberly A Kerns

ABSTRACT
Background: It is often said that children with Fetal Alcohol Spectrum Disorder (FASD) have difficulty learning from reinforcement. However, there is little empirical evidence to support or deny this claim.

Objectives: To examine reinforcement learning in children with FASD, specifically: (1) the rate of learning from reinforcement; and (2) the impact of concreteness of the reinforcer.

Methods: Participants included 18 children with FASD (IQ ≥ 70), ages 11-17, and 18 age- and sex-
matched controls. Participants each completed a novel reinforcement learning discrimination task that involved visual probabilistic learning (70% contingent feedback). The task was completed twice, once with tokens, and once with points (counterbalanced).

**Results:** The control group demonstrated significantly stronger overall reinforcement learning, although rates of improvement and effect of concreteness of the reinforcer (tokens vs. points) were not different between groups. The FASD group's responses were more likely to be guided by the most recent information, rather than based on integration of reward status over multiple trials.

**Conclusions:** Reinforcement learning does not appear to occur in a functionally different manner in children with FASD, but does take longer, and is more impacted by recent reward than an integration of overall reinforcement information. Children with FASD without an intellectual disability may be able to learn from reinforcement given sufficient consistent repetition. However, other failures associated with learning difficulties such as the complexity of the material, transfer of learning, or impulsivity were not addressed in this study.

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73) EXECUTIVE FUNCTIONING AND WORKING MEMORY DEFICITS ON THE CANTAB® AMONG CHILDREN WITH PRENATAL ALCOHOL EXPOSURE
Carmen Rasmussen, Maryam Soleimani, Jacqueline Pei

**ABSTRACT**

**Background:** Children with prenatal alcohol exposure (PAE) and Fetal Alcohol Spectrum Disorders (FASD) display numerous neuropsychological impairments, including deficits on measures of executive functioning (EF) and working memory.

**Objectives:** The goal of this project was to examine whether children with PAE and FASD demonstrate EF and working memory deficits on the CANTAB® (a computerized neuropsychological test).

**Methods:** Twenty-four children with PAE and 26 control children were tested on the CANTAB®.

**Results:** Children with PAE demonstrated deficits in the areas of executive functioning, working memory, and attention. Among the PAE group, those with FASD were specifically impaired on working memory capacity.

**Conclusions:** The CANTAB® is a useful tool for detecting neurobehavioral deficits in children with PAE.

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Aims: To systematically review the literature on the Chinese translations of the Alcohol Use Disorders Identification Test (AUDIT) and their cross-cultural applicability in Chinese language populations.

Methods: We identified peer-reviewed articles published in English (n = 10) and in Chinese (n = 11) from 1980 to September 2009, with key words China, Chinese and AUDIT among PubMed, EBSCO, PsycInfo, FirstSearch electronic databases and two Chinese databases.

Results: Five teams from Beijing, Tibet, Taiwan and Hong Kong reported their region-specific translation procedures, cultural adaptations, validity (0.93–0.95 in two versions) and reliability (0.63–0.99). These Chinese translations and short versions demonstrated relatively high sensitivity (0.880–0.997) and moderate specificity (0.709–0.934) for hazardous/harmful drinking and alcohol dependence, but low specificity for alcohol dependence among Min-Nan Taiwanese (0.58). The AUDIT and its adaptations were most utilized in workplace- and hospital-settings for screening and brief intervention. However, they were under-utilized in population-based surveys, primary care settings, and among women, adolescents, rural-to-urban migrants, the elderly and minorities. Among 12 studies from mainland China, four included both women and men, and only one in Tibet was published in English.

Conclusion: There is a growing amount of psychometric, epidemiologic and treatment research using Chinese translations of the AUDIT, much of it still unavailable in the English-language literature. Given the increase in burden of disease and injury attributable to alcohol use in the Western Pacific region, the use of an internationally comparable instrument (such as the AUDIT) in research with Chinese populations presents a unique opportunity to expand clinical and epidemiologic knowledge about alcohol problem epidemics.

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http://alcalc.oxfordjournals.org/content/early/2011/04/04/alcalc.agr012.abstract?sid=1c9490f7-fe1b-46d4-a3fa-2ff01b3b5e7b

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75) ROLE OF NEUROTROPHINS ON POSTNATAL NEUROGENESIS IN THE THALAMUS: PRENATAL EXPOSURE TO ETHANOL
Mooney SM, Miller MW.
Department of Neuroscience and Physiology, State University of New York Upstate Medical University, Syracuse, NY 13210, USA; Developmental Exposure Alcohol Research Center, State University of New York, Binghamton, NY 13902; Cortland, NY 13054; Syracuse, NY 13210, USA.

ABSTRACT
A second wave of neuronal generation occurs in the ventrobasal nucleus of the rat thalamus (VB) during the first three postnatal weeks. The present study tested the hypotheses (1) that postnatal neurogenesis in the VB is neurotrophin-regulated and (2) that ethanol-induced changes in this proliferation are mediated by neurotrophins. The first studies examined the effects of neurotrophins on the numbers of cycling cells in ex vivo preparations of the VB from 3-day-old rats. The proportion of cycling (Ki-67-positive) VB cells was higher in cultured thalamic slices treated with neurotrophins than in controls. Interestingly, this increase occurred with nerve growth factor (NGF) alone or with a combination of NGF and brain-derived neurotrophic factor (BDNF), but not with BDNF alone. Based on these data, the VBs from young offspring of pregnant rats fed an ethanol-containing or an isocaloric non-alcoholic liquid diet were examined between postnatal day (P) 1 and P31. Studies used enzyme-linked immunosorbent assays and immunoblots to explore the effects of ethanol on the expression of neurotrophins, their receptors, and representative signaling proteins. Ethanol altered the expression of neurotrophins and receptors throughout the first postnatal month. Expression of NGF increased, but there was no change in the expression of BDNF. The high affinity receptors (TrkA and TrkB) were unchanged but ethanol decreased expression of the low affinity receptor, p75. One downstream signaling protein, extracellular signal-regulated kinase (ERK), decreased but Akt expression was unchanged. Thus, postnatal cell proliferation in the VB of young rat pups is neurotrophin-responsive and is affected by ethanol.


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76) WHAT CHOLINE METABOLISM CAN TELL US ABOUT THE UNDERLYING MECHANISMS OF FETAL ALCOHOL SPECTRUM DISORDERS
Zeisel SH.
Department of Nutrition, UNC Nutrition Research Institute at Kannapolis, University of North Carolina at Chapel Hill, 500 Laureate Way, Room 2218, Kannapolis, NC, 28081, USA, steven.zeisel@unc.edu.

ABSTRACT
The consequences of fetal exposure to alcohol are very diverse and the likely molecular mechanisms involved must be able to explain how so many developmental processes could go awry. If pregnant rat dams are fed alcohol, their pups develop abnormalities characteristic of fetal alcohol spectrum disorders (FASD), but if these rat dams were also treated with choline, the effects from ethanol were attenuated in their pups. Choline is an essential nutrient in humans, and is an important methyl group donor. Alcohol exposure disturbs the metabolism of choline and other methyl donors. Availability of choline during gestation directly influences epigenetic marks on DNA and histones, and alters gene expression needed for normal neural and endothelial progenitor cell proliferation. Maternal diets low in choline alter development of the mouse hippocampus, and decrement memory for life. Women eating choline during pregnancy have fewer children with FASD.
low-choline diets have an increased risk of having an infant with a neural tube or orofacial cleft birth defect. Thus, the varied effects of choline could affect the expression of FASD, and studies on choline might shed some light on the underlying molecular mechanisms responsible for FASD.

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Abnormalities in early brain development have been linked to Fetal Alcohol Spectrum Disorders (FASD). This review summarizes the most recent research on the neurodevelopmental abnormalities of FASD using magnetic resonance imaging (MRI). The findings suggest that FASD is associated with a range of structural and functional changes in the brain. These abnormalities may be related to the prenatal alcohol exposure and could contribute to the cognitive and behavioral difficulties seen in children with FASD.

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78) PRENATAL ALCOHOL EXPOSURE IS ASSOCIATED WITH CONDUCT DISORDER IN ADOLESCENCE: FINDINGS FROM A BIRTH COHORT
Larkby CA, Goldschmidt L, Hanusa BH, Day NL.
Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213-2593, USA. larkby@pitt.edu

ABSTRACT
Objective: To evaluate the association between prenatal alcohol exposure and the rate of conduct

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disorder in exposed compared with unexposed adolescents.

**Method:** Data for these analyses are from a longitudinal study of prenatal substance exposures. Women were interviewed at their fourth and seventh prenatal months, and with their children, at birth, 8 and 18 months, 3, 6, 10, 14, and 16 years postpartum. Offspring were interviewed with the Diagnostic Interview Schedule-IV; maternal and adolescent diagnoses were made using DSM-IV criteria at age 16 years. The sample was 592 adolescents and their mothers or caretakers.

**Results:** Prenatal alcohol exposure is significantly associated with an increased rate of conduct disorder in the adolescents. This effect was detected above an average exposure of one or more drinks per day in the first trimester. The effect remained significant after controlling for other significant variables including measures of the environment, maternal psychopathology, and other prenatal exposures.

**Conclusion:** Prenatal alcohol use in the first trimester is a risk factor for conduct disorder in the exposed offspring.

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84) **SELECTIVE UNDEREXPRESSION OF KV3.2 AND KV3.4 CHANNELS IN THE CORTEX OF RATS EXPOSED TO ETHANOL DURING EARLY POSTNATAL LIFE**
Tavian D, De Giorgio A, Granato A.

Department of Psychology, Catholic University, Largo A. Gemelli 1, 20123, Milan, Italy.

**ABSTRACT**
The expression of voltage-gated potassium channels belonging to the Kv3 family has been studied in the sensori-motor cortex of rats exposed to alcohol inhalation during the first postnatal week (P2-P6). The study was carried out using comparative RT-PCR. At P9, a significant reduction of the expression of Kv3.2 and Kv3.4 subunits occurred in alcohol-treated animals, as compared with controls. The expression of the Kv3.4a splicing variant, which is thought to be critically involved in the high-frequency firing of some cortical interneurons, was also correspondingly reduced. The downregulation of Kv3.2 and Kv3.4a subunits represented a long-lasting effect of alcohol exposure, since it was also observed in P24 animals. The expression of both Kv3.1 and Kv3.3 channels appeared to be not significantly affected by alcohol exposure. An increased susceptibility to apoptotic neuronal death after early postnatal exposure to ethanol was confirmed by the lower bcl-2/bax ratio observed in alcohol-treated animals. Although Kv3.4 subunits are thought to trigger apoptosis, the lack of upregulation in our model argues against their involvement in the mechanism leading to alcohol-induced apoptosis. The possible consequences of the selective downregulation of Kv3 subunits on the cortical function, as well as their relevance for the genesis of fetal alcohol effects, are discussed.

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ALCOHOL ALTERS DNA METHYLATION PATTERNS AND INHIBITS NEURAL STEM CELL DIFFERENTIATION

Zhou FC, Balaraman Y, Teng M, Liu Y, Singh RP, Nephew KP. From the Department of Anatomy and Cell Biology (FCZ, YB, RPS); Stark Neuroscience Research Institute (FCZ); Department of Medical and Molecular Genetics (MT, YL); Center for Computational Biology and Bioinformatics (MT, YL); Center for Medical Genomics (MT, YL); Medical Sciences Program and Department of Cellular & Integrative Physiology (KPN); Institute of Psychiatric Research (YB), Indiana University School of Medicine, Indianapolis, Indiana; and School of Computer Science and Technology (MT), Harbin Institute of Technology, Harbin, Heilongjiang, China.

ABSTRACT

Background: Potential epigenetic mechanisms underlying fetal alcohol syndrome (FAS) include alcohol-induced alterations of methyl metabolism, resulting in aberrant patterns of DNA methylation and gene expression during development. Having previously demonstrated an essential role for epigenetics in neural stem cell (NSC) development and that inhibiting DNA methylation prevents NSC differentiation, here we investigated the effect of alcohol exposure on genome-wide DNA methylation patterns and NSC differentiation.

Methods: Neural stem cells in culture were treated with or without a 6-hour 88 mM (“binge-like”) alcohol exposure and examined at 48 hours, for migration, growth, and genome-wide DNA methylation. The DNA methylation was examined using DNA-methylation immunoprecipitation followed by microarray analysis. Further validation was performed using Independent Sequenom analysis.

Results: Neural stem cell differentiated in 24 to 48 hours with migration, neuronal expression, and morphological transformation. Alcohol exposure retarded the migration, neuronal formation, and growth processes of NSC, similar to treatment with the methylation inhibitor 5-aza-cytidine. When NSC departed from the quiescent state, a genome-wide diversification of DNA methylation was observed—that is, many moderately methylated genes altered methylation levels and became hyper- and hypomethylated. Alcohol prevented many genes from such diversification, including genes related to neural development, neuronal receptors, and olfaction, while retarding differentiation. Validation of specific genes by Sequenom analysis demonstrated that alcohol exposure prevented methylation of specific genes associated with neural development [cut-like 2 (cutl2), insulin-like growth factor 1 (Igf1), epidermal growth factor-containing fibulin-like extracellular matrix protein 1 (Efemp1), and SRY-box-containing gene 7 (Sox 7)]; eye development, lens intrinsic membrane protein 2 (Lim 2); the epigenetic mark Smarca2 (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2); and developmental disorder [DiGeorge syndrome critical region gene 2 (Dgcr2)]. Specific sites altered by DNA methylation also correlated with transcription factor binding sites known to be critical for regulating neural development.

Conclusion: The data indicate that alcohol prevents normal DNA methylation programming of key neural stem cell genes and retards NSC differentiation. Thus, the role of DNA methylation in FAS warrants further investigation.


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81) CONCEIVING RISK, DIVERGENT RESPONSES: PERSPECTIVES ON THE CONSTRUCTION OF RISK OF FASD IN SIX COUNTRIES
Drabble LA, Poole N, Magri R, Tumwesigye NM, Li Q, Plant M.
1 San Jose State University, School of Social Work, San Jose, California, USA.

ABSTRACT
Conceptualizations of risks related to women's alcohol use during pregnancy, and the attendant response to preventing fetal alcohol spectrum disorder (FASD), are examined in six countries: the United States, Canada, the United Kingdom, Uganda, Uruguay, and China. Considerable differences were found in how risks were conceptualized across countries and in contextual factors that influence research, prevention, and intervention efforts. Differences in conceptualizations were also apparent within countries. Differences also existed in the degree to which the issue of drinking during pregnancy has been minimized or amplified and in whether and how responses are linked to treatment or other public health interventions.


82) PREVALENCE AND PREDICTORS OF ALCOHOL USE IN PREGNANCY AND BREASTFEEDING AMONG AUSTRALIAN WOMEN.
Maloney E, Hutchinson D, Burns L, Mattick RP, Black E.
National Drug and Alcohol Research Centre, University of New South Wales, Sydney, New South Wales, Australia.

ABSTRACT
Background: Previous research suggests that alcohol use during pregnancy and breastfeeding has a negative impact on birth and neonatal outcomes. No threshold for this effect has been determined. The aim of this study is to determine the prevalence and correlates of alcohol use in pregnancy and lactation in a large representative sample of Australian women.

Method: Data were used from a large representative sample of Australian women drawn from the 2007 National Drug Strategy Household Survey. A complex sampling framework was used to elicit prevalence estimates for alcohol use during pregnancy and lactation. A logistic regression analysis was used to determine the psychosocial characteristics associated with alcohol use during the perinatal period.

Results: Alcohol use was reported by 29 percent of women who were pregnant in the past 12 months. In addition, 43 percent of women who were breastfeeding in the past 12 months reported alcohol use, whereas 36 percent of women who were both pregnant and breastfeeding in the past 12 months reported alcohol use. Most women (95%) reported a reduction in the quantity of their alcohol use while pregnant or breastfeeding. Older age was significantly associated with alcohol use in pregnancy, and also with alcohol use while breastfeeding (after controlling for other psychosocial characteristics). Higher educational attainment, and breastfeeding for more weeks in the past 12 months were significantly associated with alcohol use while breastfeeding, after controlling for confounding psychosocial factors.
Conclusions: More research is needed to ease uncertainty about "safe" levels of alcohol use during pregnancy and while breastfeeding. A high proportion of the sample reported alcohol use during pregnancy or lactation, despite uniform international government guidelines recommending that no alcohol should be consumed during the prenatal and postnatal periods. These results indicate that public health education campaigns about the risks of alcohol during these periods are needed.


83) AGOG COMMITTEE OPINION NO. 473: SUBSTANCE ABUSE REPORTING AND PREGNANCY: THE ROLE OF THE OBSTETRICIAN-GYNECOLOGIST
American College of Obstetricians and Gynecologists Committee on Health Care for Underserved Women.

ABSTRACT
Drug enforcement policies that deter women from seeking prenatal care are contrary to the welfare of the mother and fetus. Incarceration and the threat of incarceration have proved to be ineffective in reducing the incidence of alcohol or drug abuse. Obstetrician–gynecologists should be aware of the reporting requirements related to alcohol and drug abuse within their states. They are encouraged to work with state legislators to retract legislation that punishes women for substance abuse during pregnancy.


84) SMOKING AND ALCOHOL USE DURING PREGNANCY AND AGE OF MENARCHE IN DAUGHTERS
Shrestha A, Nohr EA, Bech BH, Ramlau-Hansen CH, Olsen J.
Department of Epidemiology, School of Public Health, UCLA, Los Angeles, CA 90095-1772, USA. ashrestha@mednet.ucla.edu

ABSTRACT
Background: We assessed whether exposure to prenatal smoking or alcohol accelerates age of menarche (AOM) in offspring.

Methods: We studied a Danish cohort of 3169 singleton females born in April 1984-April 1987. Linear regressions were conducted to examine associations between prenatal smoking or alcohol exposure and offspring’s AOM on: (i) the daughters who provided data on both month and the year of menarche (n= 1634) and (ii) the entire sample that provided at least the year of menarche (n= 3169). We also examined associations between only pre-pregnancy smoking or childhood exposure to smoking and AOM. The full model was adjusted for maternal pre-pregnancy body mass index, maternal age at childbirth, parental socio-economic status, parity, consumption of milk products during pregnancy and marital status.
**Results:** Among those who provided both year and month, AOM was accelerated by 2.8 months (95% CI in months: -5.3, -0.4) among those exposed to 10+ cigarettes/day throughout pregnancy and by 4.1 months (95% CI in months: -7.7, -0.5) among those with mothers who quit smoking sometime during pregnancy, compared with the unexposed group after adjustment for covariates. Similar, but much weaker, associations were observed among girls whose mothers smoked 1-9 cigarettes/day throughout pregnancy or whose fathers smoked compared with their unexposed counterparts after adjustment for covariates [-0.8 months (95% CI: -2.6, 1.0)]. No associations were observed between AOM and only pre-pregnancy smoking or only childhood exposure or prenatal alcohol exposure.

**Conclusions:** Our study indicates that heavy smoking throughout the pregnancy may be important in prenatal programming of AOM.


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FETAL EXPOSURE TO TERATOGENS: EVIDENCE OF GENES INVOLVED IN AUTISM
Dufour-Rainfray D, Vourc'h P, Tourlet S, Guilloteau D, Chalon S, Andres CR.
UMR INSERM U930, CNRS ERL 3106, Université François Rabelais de Tours, Tours, France.
diane.dufour@univ-tours.fr

ABSTRACT
Environmental challenges during the prenatal period can result in behavioral abnormalities and cognitive deficits that appear later in life such as autism. Prenatal exposure to valproic acid, ethanol, thalidomide and misoprostol has been shown to be associated with an increased incidence of autism. In addition, rodents exposed in utero to some of these drugs show autism-like abnormalities, including brain changes and lifelong behavior dysfunction. Our aim is to summarize current understanding of the relationship between in utero exposure to these drugs and autism in humans and in autism-like animal model phenotypes. It also highlights the importance of these models to understanding the neurobiology of autism, particularly in the identification of susceptibility genes. These drugs are able to modulate the expression of many genes involved in processes such as proliferation, apoptosis, neuronal differentiation and migration, synaptogenesis and synaptic activity. It seems essential to focus research on genes expressed during early neurodevelopment which may be the target of mutations or affected by drugs such as those included in this review.

Link to the Article,

87) MEASURING COSTS OF ALCOHOL HARM TO OTHERS: A REVIEW OF THE LITERATURE
Navarro HJ, Doran CM, Shakeshaft AP.
National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW 2052, Australia.

ABSTRACT
Introduction: People other than the drinker experience harmful consequences from alcohol misuse, accounting for part of the economic burden to society. Little has been done on costing harm to others.

Aims:
Method: A literature review was undertaken of various databases, government publications, dissertations, conference papers and reference materials. Publications were included for analysis if they reported costs on alcohol harm to others. Methodological adequacy of costing studies was assessed using a checklist modified from the Drummond 10-point checklist.

Results: In total, 25 publications including costs on alcohol harm to others were reviewed. Fetal alcohol syndrome (FAS) was the harm to others most frequently cost. The cost-of-illness (COI) framework was used in 24 of the publications, while 1 employed a cost-benefit analysis (CBA) serving as starting point for further studies estimating intangible costs (e.g. victim's quality-of-life (QoL) loss). Indirect costs (e.g. victim's lost productivity) were quantified most frequently with the human capital approach. The majority of publications critically assessed on costing received an average quality score (17/25).

Conclusion: Few studies have reported costs on the magnitude from harm to people other than the...
drinker, therefore the overall economic burden of risky alcohol consumption across countries is underestimated. This review may be considered a starting point for future research on costing alcohol harm to others.

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88) ALCOHOL RESEARCH: PAST, PRESENT, AND FUTURE
Gunzerath L, Hewitt BG, Li TK, Warren KR.
National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Rockville, Maryland 20892, USA. lg72x@nih.gov

ABSTRACT
Created forty years ago, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) has played a major role in the great strides made in the understanding, treatment, prevention, and public acceptance of alcohol-use disorders. Throughout most of U.S. history "habitual drunkenness" was viewed as a problem of moral degeneracy or character flaw inherent in the individual. However, the wealth of scientific evidence amassed throughout NIAAA's history has established alcoholism as a medical condition, that is, as a disease for which affected individuals should feel no shame or be treated with disdain. We look at the developments in alcohol epidemiology, typology, etiology, prevention, and treatment research over the past 40 years. We also discuss how NIAAA addresses alcohol disorders from a life-course framework, affecting all stages of the lifespan, from fetus through child, adolescent, and young adult, to midlife/senior adult, with each stage involving different risks, consequences, prevention efforts, and treatment strategies.

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89) CELLULAR AND MITOCHONDRIAL EFFECTS OF ALCOHOL CONSUMPTION
Manzo-Avalos S, Saavedra-Molina A.
Instituto de Investigaciones Quimico-Biologicas, Universidad Michoacana de San Nicolas de Hidalgo, Edificio B-3. C.U., 58030 Morelia, Michoacan, Mexico. smanzo@umich.mx

ABSTRACT
Alcohol dependence is correlated with a wide spectrum of medical, psychological, behavioral, and social problems. Acute alcohol abuse causes damage to and functional impairment of several organs affecting protein, carbohydrate, and fat metabolism. Mitochondria participate with the conversion of acetaldehyde into acetate and the generation of increased amounts of NADH. Prenatal exposure to ethanol during fetal development induces a wide spectrum of adverse effects in offspring, such as neurologic abnormalities and pre- and post-natal growth retardation. Antioxidant effects have been described due to that alcoholic beverages contain different compounds, such as polyphenols as well as resveratrol. This review analyzes diverse topics on the alcohol consumption effects in several
human organs and demonstrates the direct participation of mitochondria as potential target of compounds that can be used to prevent therapies for alcohol abusers.

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90) PRECONCEPTIONAL ALCOHOLIC INTOXICATION ALTERS THE DISTRIBUTION OF METALS IN MATURED RAT BRAIN OF OFFSPRING
Vyatchanina ES.

ABSTRACT
It is known that alcohol possesses embryotoxic, teratogenic, neurotoxic and other effects. Alteration of the trace element and mineral metabolism can be one of the triggering mechanisms of metabolic changes during an alcoholic intoxication. The aim of the recent study was to compare the profiles of elements in brain structures of matured offspring which were born by female rats exposed and non-exposed to alcohol before conception. A decreasing tendency in the levels of all detected macro and trace elements in four brain structures was observed. The most prominent changes were found in the brain cortex. Experimental data show that short term consumption of alcohol by female rats before pregnancy alters the distribution of macro and trace elements in the offspring's brain structures.

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91) NUMBER PROCESSING IN ADOLESCENTS WITH PRENATAL ALCOHOL EXPOSURE AND ADHD: DIFFERENCES IN THE NEUROBEHAVIORAL PHENOTYPE
Jacobson JL, Dodge NC, Burden MJ, Korman R, Jacobson SW.
From the Department of Psychiatry and Behavioral Neurosciences (JLJ, NCD, MJB, SWJ), Wayne State University School of Medicine, Detroit, Michigan; Department of Clinical and Social Sciences in Psychology (RK), University of Rochester, Rochester, New York.

ABSTRACT
Background: Poor arithmetic performance is among the most sensitive outcomes associated with prenatal alcohol exposure and is also common in individuals with attention-deficit hyperactivity disorder (ADHD). We hypothesized that prenatal alcohol exposure would be associated with deficits in the most fundamental aspects of number processing, representation of quantity and distance, whereas ADHD would be associated with deficits in calculation, the form of number processing most dependent on attention and memory.

Methods: Two hundred and sixty-two inner-city, African American adolescents, who had been evaluated prospectively for prenatal alcohol exposure and ADHD, were assessed on a number-processing test comprised of 7 subtests.

Results: More heavily alcohol-exposed adolescents were 4 times more likely to meet diagnostic
criteria for ADHD than those whose mothers abstained from alcohol use during pregnancy. Two dimensions of number processing were identified in a factor analysis-magnitude comparison and calculation. As hypothesized, prenatal alcohol exposure was more strongly related to the former and ADHD to the latter. Moreover, the relation of prenatal alcohol to calculation was fully mediated by magnitude comparison, whereas the relation of ADHD to calculation was mediated by IQ but not by magnitude comparison.

Conclusion: These data confirm findings from previous studies identifying arithmetic as a particularly sensitive developmental endpoint for prenatal alcohol exposure. Whereas difficulties with arithmetic in ADHD are mediated by domain-general deficits in overall cognitive ability, fetal alcohol-related arithmetic difficulties are mediated primarily by a specific deficit in the core quantity system involving the ability to mentally represent and manipulate number. These data suggest that different interventions are likely to be effective for remediating arithmetic problems in children with prenatal alcohol exposure than in non-exposed children with ADHD.


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92) EXPOSURE TO ETHANOL DURING THE LAST TRIMESTER OF PREGNANCY ALTERS THE MATURATION AND IMMUNITY OF THE FETAL LUNG
Lazic T, Sow FB, Van Geelen A, Meyerholz DK, Gallup JM, Ackermann MR.
Department of Veterinary Pathology, College of Veterinary Medicine, Iowa State University, Ames, IA 50011-1250, USA.

ABSTRACT
The effects of ethanol exposure on fetal lungs remain under investigation. Previously, we demonstrated that lambs exposed to ethanol during gestation had impaired expression of pulmonary surfactant protein A, a crucial component of lung immunity. In this study, we investigated the effects of in utero exposure to ethanol on maturation and immunity of the fetal lung. Pregnant ewes were surgically implanted with an abomasal cannula and administered 1g ethanol/kg (n=8) or water (n=8) during the last trimester of pregnancy. Lambs were delivered prematurely or naturally. Neonatal lungs were assessed for maturation markers (hypoxia-inducible factor-1α [HIF-1α], HIF-2α, HIF-3α, vascular endothelial growth factor-A [VEGF-A], VEGFR-1, VEGFR-2, glycogen, and lung protein levels) and immunity (cytokines and chemokines). Preterm animals exposed to ethanol had significantly reduced VEGF-A mRNA (P=.066) and protein levels, HIF-1α (P=.055), HIF-2α (P=.019), VEGFR-1 (P=.088), and VEGFR-2 (P=.067) mRNA levels but no changes in HIF-3α mRNA. No significant changes occurred in full-term animals exposed to ethanol. Glycogen levels were significantly higher in preterm animals exposed to ethanol (P=.006) but not in full-term animals. Ethanol exposure was associated with significantly lower lung protein levels in preterm (P=.03) but not full-term animals. Preterm animals exposed to ethanol had significantly reduced TNF-α (P=.05), IL-10 (P=.03), chemokine (C-C motif) ligand 5 (CCL5) (P=.017), and monocyte chemotactic protein-1 (MCP-1) (P=.0004) mRNA. In full-term animals exposed to ethanol, the immune alterations were either sustained (TNF-α, P=.009; IL-10, P=.03) or returned to near baseline levels (CCL5 and MCP-1). The ethanol-mediated alterations in fetal lung maturation and immunity may explain the increased incidence of respiratory infections in...
neonates exposed to ethanol in utero.

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93) PRENATAL ALCOHOL EXPOSURE – A SYSTEMATIC REVIEW OF THE EFFECTS ON CHILD MOTOR FUNCTION  
Bjørn Bay, Ulrik Schiøler Kesmodel

ABSTRACT

Methods: The search strategy included Medline, Embase, The Cochrane Library and Scopus. The authors read titles and abstracts, and the articles that met the predefined criteria for inclusion were obtained and the full text read. The articles were assessed for quality using the Newcastle–Ottawa Quality Assessment Scale.

Main outcome measures: Motor function measured on standardized or validated tests. Results. The search resulted in 311 titles and abstracts, of which 39 were found relevant for inclusion. The findings of this review suggest a negative effect when the maternal consumption exceeded a certain level. Of all studies reporting a maternal intake of more than four drinks/day, only one study showed no effect on motor function, and of all studies reporting intake levels of less than 10 drinks/week, only one study showed deficit on the children's motor function.

Conclusions: While it appears consistent that high daily alcohol intake is associated with deficits in gross and fine motor function, and low weekly intake is not associated with such deficits, the issue of binge drinking is unsettled.

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94) PARAMETERIZATION-IN Variant SHAPE COMPARISONS OF ANATOMICAL SURFACES  
Department of Statistics, Florida State University, Tallahassee, FL 32306, USA. skurtek@stat.fsu.edu

ABSTRACT
We consider 3-D brain structures as continuous parameterized surfaces and present a metric for their comparisons that is invariant to the way they are parameterized. Past comparisons of such surfaces
involve either volume deformations or nonrigid matching under fixed parameterizations of surfaces. We propose a new mathematical representation of surfaces, called q-maps, such that distances between such maps are invariant to re-parameterizations. This property allows for removing the parameterization variability by optimizing over the re-parameterization group, resulting in a proper parameterization-invariant distance between shapes of surfaces. We demonstrate this method in shape analysis of multiple brain structures, for 34 subjects in the Detroit Fetal Alcohol and Drug Exposure Cohort study, which results in a 91% classification rate for attention deficit hyperactivity disorder cases and controls. This method outperforms some existing techniques such as spherical harmonic point distribution model (SPHARM-PDM) or iterative closest point (ICP).

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95) CANDIDATE PLACENTAL BIOMARKERS FOR INTRAUTERINE ALCOHOL EXPOSURE
Shukla PK, Sittig LJ, Ullmann TM, Redei EE.
From the Department of Psychiatry and Behavioral Sciences, The Asher Center, Feinberg School of Medicine, Northwestern University, Chicago, Illinois.

ABSTRACT
Background: Fetal alcohol spectrum disorder (FASD) is a leading cause of nongenetic mental retardation and other neurodevelopmental deficits. Earlier diagnosis of FASD would greatly improve prognosis for individuals and families affected by this disorder. Here, we identify candidate placental biomarkers in an animal model of FASD that recapitulates many aspects of human FASD.

Methods: Pregnant Sprague-Dawley (SD) females were assigned to 1 of 3 diet groups on gestation day 8 (G8): Ethanol (E), Pair-fed (PF) or Control (C). E dams received ethanol-containing liquid diet and PF dams received isocaloric liquid diet in an amount that matched the paired E dam’s diet consumption the previous day. Control dams received laboratory chow and water ad libitum. Whole placenta from individual fetuses were collected on gestational day 21 (G21) for analyses. Western blotting and quantitative real-time RT-PCR were used to measure protein and mRNA levels of placental iodothyronine deiodinase III (Dio3), thyroid hormone receptor α1 (TRα1), and glucocorticoid receptor (GR). Placental mRNA levels of intrauterine growth restriction (IUGR) markers Igf-2, Phlda2, and Cdkn1c were also measured.

Results: Placental protein and mRNA levels from ethanol (E)-consuming dams showed the following changes: increased Dio3, decreased TRα1, and decreased GR compared to both C and PF dams. Placental mRNA levels of intrauterine growth restriction (IUGR) markers Igf-2, Phlda2, and Cdkn1c were altered similarly in PF and E dams.

Conclusions: We propose the specific pattern of increased Dio3 and decreased TRα1 and GR protein levels in the placenta as selective biomarker for intrauterine alcohol exposure.

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96) VITAMIN C PROTECTS AGAINST ETHANOL AND PTZ-INDUCED APOPTOTIC NEURODEGENERATION IN PRENATAL RAT HIPPOCAMPAL NEURONS

Naseer MI, Ullah N, Ullah I, Koh PO, Lee HY, Park MS, Kim MO.
Division of Life Science, College of Natural Sciences (RINS) and Applied Life Science (BK 21), Gyeongsang National University, Chinju 660-701, Republic of Korea.

ABSTRACT
Exposure to alcohol during brain development may cause a neurological syndrome called fetal alcohol syndrome, characterized by pre- and postnatal growth deficiencies, craniofacial anomalies, and evidence of CNS dysfunction. The objective of this study was to evaluate pentylenetetrazol (PTZ) and ethanol effects on Bax, Bcl-2 expression, which further induced activation of caspase-3, release of cytochrome-c from mitochondria, and to observe the protective effects of vitamin C (vit-C) against PTZ and ethanol-induced apoptotic neurodegeneration in primary-cultured neuronal cells at gestational day 17.5. Apoptotic neurodegeneration and neuroprotective effect of vit-C were measured by using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenly tetrazolium bromide assay, Western blot analysis, which further conformed by the measurement of mitochondrial membrane potential using JC-1 detection kit and immunofluorescence analysis. The results showed that PTZ and ethanol produced extensive Bax-dependent caspase -9 and caspase-3 activation and caused neuronal apoptosis. Furthermore, the cotreatment of vit-C along with ethanol and PTZ showed significantly decreased expression of Bax, caspase-9, caspase-3, cytochrome-c, and significantly increased expression of antiapoptotic Bcl-2 protein when compared with control group. Our findings indicate that PTZ and ethanol activate an intrinsic apoptotic death program in neurons that is likely to contribute to the neuropathologic effects in fetal alcohol exposure, and vit-C can prevent some of the deleterious effects of PTZ and ethanol on the developing brain. The available experimental evidence and the safety of vit-C in pregnancy suggest the experimental use of ascorbic acid as a new and effective protective agent ethanol and PTZ-induced apoptotic neurodegeneration.

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who drank alcohol 3 months prior to conception were 3 times more likely to develop abruptio placentae than the control group (OR 3.06, p=0.003). Drinking alcoholic beverages during pregnancy carried a more than 3 times greater risk of developing abruptio placentae (OR 3.52, p=0.0006). In the study group, women consumed a mean of 13.6, 12.0 and 11.2 standard drinks in a typical week at 12 and 3 months before and during pregnancy, respectively. The study group demonstrated a binge-drinking pattern, with two to four sessions per month.

**Conclusion**: An association was found between preconception and prenatal consumption of alcohol and abruptio placentae.

**Link to the Article**,  

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**98) YOUNG CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER--COMMUNICATION PROFILES**  
De Beer M, Kritzinger A, Zsilavecz U.  
Department of Communication Pathology, University of Pretoria. [mari.debeer@up.ac.za](mailto:mari.debeer@up.ac.za)

**ABSTRACT**  
The aim of the article is to describe the communication profiles of five young children with fetal alcohol spectrum disorder (FASD) from 4 to 58 months of age. A collective case-study design following a quantitative and descriptive approach was used to describe the communication profiles of the participants. The results are described according to the participants' case histories and a four-level early communication assessment framework. The significant findings were that all participants were in foster care, and presented with incomplete case histories, general developmental delays and delays regarding all aspects of their communication abilities. An increase in the severity of the spectrum disorder across the participants' combined communication profiles was also identified. Participants presented with complex multiple neurodevelopmental needs that should be viewed within a developmental systems and ecological framework. The importance of early identification, diagnosis and assessment of infants and young children prenatally exposed to alcohol, the identification of precursors to communication impairment at a very early age, and the need for individualised early communication intervention to improve developmental outcomes within a family-centred approach are discussed. Suggestions for future research to accumulate knowledge about FASD in the field of early communication intervention are made.

**Link to the Article**,  

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**99) BRAIN DISORDERS IN FETAL ALCOHOL SYNDROME**  
Shilko VI, Malakhova ZhL, Bubnov AA.  
Department of Children Disease, Therapy and Prevention Faculty, Ural State Medical Academy, Federal Agency for Health Care and Social Development, Ekaterinburg, Russia.

**ABSTRACT**  
Intrauterine effect of alcohol on the development of cytomorphological structure of CNS in rats was
studied by heterogeneous enzyme-linked immunosorbent assay. The level of transforming growth factor-β1 (TGF-β1) in animals during pregnancy was analyzed. Pronounced damaging effect of alcohol on brain cell in the progeny of alcoholized animals was demonstrated: loosening of nerve cells and degenerative changes in the form of pyknosis and chromatolysis in the cortex, hypothalamus, and cerebellum; subtotal decrease (sometimes complete absence) of neuroendocrine granules. The level of TGF-β1 was significantly increased in alcoholized pregnant females, which can attest to defects of the receptor apparatus of the target cells in both females and the progeny. Thus, the observed peculiarities of TGF-β1 expression are comparable to morphological changes in the brain and can be extrapolated to similar processes in humans (fetal alcohol syndrome).

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100) COMMUNICATING THE RISKS OF FETAL ALCOHOL SPECTRUM DISORDER: EFFECTS OF MESSAGE FRAMING AND EXEMPLIFICATION
Yu N, Ahern LA, Connolly-Ahern C, Shen F.
Department of Communication, North Dakota State University, USA. nan.yu@ndsu.edu

ABSTRACT
Health messages can be either informative or descriptive, and can emphasize either potential losses or gains. This study, guided by message framing theory and exemplification theory, specifically investigated the combined effects of messages with loss-gain frames mixed with statistics or exemplar appeals. The findings revealed a series of main effects and interactions for loss-gain frames and statistics-exemplar appeals on fetal alcohol spectrum disorder (FASD) prevention intention, intention to know more, perceived severity, perceived fear, perceived external efficacy, and perceived internal efficacy. The gain-statistics appeal showed an advantage in promoting perceived efficacy toward FASD, while the loss-exemplar appeal revealed an advantage in increasing prevention intention, perceived severity, and perceived fear toward FASD. Limitations and implications for future research are discussed.

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101) LOW BIRTH WEIGHT--ADDITIONAL IMPORTANT FACTOR OF DIAGNOSIS IN CHILDREN WITH SHORT STATURE
Majcher A, Pyrzyk B, Bielecka-Jasiocha J, Witkowska-Sędek E.
Klinika Pediatrii i Endokrynologii WUM. amajcher@wum.edu.pl

ABSTRACT
Introduction: Birth parameters are one of the more important predictors of body height in adult life. Children with low birth weight (LBW) are an essential and heterogenic group of patients diagnosed because of short stature.
**Aim of the Study:** Evaluation of frequency of low birth mass in children with short stature and evaluation of anthropometric parameters in children with low and normal birth weight.

**Material and Methods:** Analysis of birth data and present somatic parameters in 802 children with short stature who were admitted to the Clinic of Paediatrics and Endocrinology. This group consisted of 456 boys and 346 girls. The mean calendar age was 9 years. Differential diagnosis of growth disorders was made. Our group contained 133 children with growth hormone deficiency (GHD) and 26 girls with Turner's syndrome. Data of birth parameters (length, weight and length of pregnancy) were collected, anthropometric measurements of children and their parents were made, body mass index (BMI) was calculated. Low birth weight (LBW) is a birth weight ≤2500 g. The values of present somatic parameters were normalized according to the references of the Institute of Mother and Child, data of parameters were given in standard deviation score.

**Results:** In the whole examined group LBW was observed in 17.3% (137 children). LBW was observed in 23% of girls with Turner's syndrome. Among the children who were born on time low birth weight was observed in 5.3% (30 children --15 boys and 15 girls). In this group there were 10 patients from a twin pregnancy, 2 with fetal alcohol syndrome and 4 with Silver-Russell syndrome. In 14 patients SGA (small for gestational age) was observed. The children with LBW contacted the clinic a year earlier than other patients, with more body height deficiency (-2.5 SDS vs. -2.1 SDS) and smaller values of BMI. No statistically significant differences between midparental height in both groups were observed.

**Conclusion:** 1. Low birth weight is diagnosed in every sixth child with short stature in the Clinic of Endocrinology. 2. Children born on time with low birth weight should be diagnosed early towards congenital genetic disorders and development defects.

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**102) STRUCTURAL, METABOLIC, AND FUNCTIONAL BRAIN ABNORMALITIES AS A RESULT OF PRENATAL EXPOSURE TO DRUGS OF ABUSE: EVIDENCE FROM NEUROIMAGING**  
Roussotte F, Soderberg L, Sowell E.  
Developmental Cognitive Neuroimaging Group, Department of Neurology, University of California, Los Angeles, CA 90095-7332, USA.

**ABSTRACT**  
Prenatal exposure to alcohol and stimulants negatively affects the developing trajectory of the central nervous system in many ways. Recent advances in neuroimaging methods have allowed researchers to study the structural, metabolic, and functional abnormalities resulting from prenatal exposure to drugs of abuse in living human subjects. Here we review the neuroimaging literature of prenatal exposure to alcohol, cocaine, and methamphetamine. Neuroimaging studies of prenatal alcohol exposure have reported differences in the structure and metabolism of many brain systems, including in frontal, parietal, and temporal regions, in the cerebellum and basal ganglia, as well as in the white matter tracts that connect these brain regions. Functional imaging studies have identified significant differences in brain activation related to various cognitive domains as a result of prenatal alcohol exposure. The published literature of prenatal exposure to cocaine and methamphetamine is much smaller, but evidence is beginning to emerge suggesting that exposure to stimulant drugs in utero may be particularly toxic to dopamine-rich basal ganglia regions. Although the interpretation of such
findings is somewhat limited by the problem of polysubstance abuse and by the difficulty of obtaining precise exposure histories in retrospective studies, such investigations provide important insights into the effects of drugs of abuse on the structure, function, and metabolism of the developing human brain. These insights may ultimately help clinicians develop better diagnostic tools and devise appropriate therapeutic interventions to improve the condition of children with prenatal exposure to drugs of abuse.


103) LIQUID-DIET WITH ALCOHOL ALTERS MATERNAL, FETAL AND PLACENTAL WEIGHTS AND THE EXPRESSION OF MOLECULES INVOLVED IN INTEGRIN SIGNALING IN THE FETAL CEREBRAL CORTEX
Rout UK, Dhossche JM.
Department of Surgery, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216, USA. urout@umc.edu

ABSTRACT
Maternal alcohol consumption during pregnancy causes wide range of behavioral and structural deficits in children, commonly known as Fetal Alcohol Syndrome (FAS). Children with FAS may suffer behavioral deficits in the absence of obvious malformations. In rodents, the exposure to alcohol during gestation changes brain structures and weights of offspring. The mechanism of FAS is not completely understood. In the present study, an established rat (Long-Evans) model of FAS was used. The litter size and the weights of mothers, fetuses and placentas were examined on gestation days 18 or 20. On gestation day 18, the effects of chronic alcohol on the expression levels of integrin receptor subunits, phospholipase-Cγ and N-cadherin were examined in the fetal cerebral cortices. Presence of alcohol in the liquid-diet reduced the consumption and decreased weights of mothers and fetuses but increased the placental weights. Expression levels of β(1) and α(3) integrin subunits and phospholipase-Cy(2) were significantly altered in the fetal cerebral cortices of mothers on alcohol containing diet. Results show that alcohol consumption during pregnancy even with protein, mineral and vitamin enriched diet may affect maternal and fetal health, and alter integrin receptor signaling pathways in the fetal cerebral cortex disturbing the development of fetal brains.


104) PRENATAL ETHANOL EXPOSURE ENHANCES NMDAR-DEPENDENT LONG-TERM POTENTIATION IN THE ADOLESCENT FEMALE DENTATE GYRUS
Titterness AK, Christie BR.
Graduate Program in Neuroscience, University of British Columbia, Vancouver, BC, Canada.

ABSTRACT
The dentate gyrus (DG) is a region of the hippocampus intimately involved with learning and memory.

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Prenatal exposure to either stress or ethanol can reduce long-term potentiation (LTP) in the male hippocampus but there is little information on how these prenatal events affect LTP in the adolescent female hippocampus. Previous studies suggest that deleterious effects of PNEE can, in part, be mediated by corticosterone, suggesting that prenatal stress might further enhance any alterations to LTP induced PNEE. When animals were exposed to a combination of prenatal stress and PNEE distinct sex differences emerged. Exposure to ethanol throughout gestation significantly reduced DG LTP in adolescent males but enhanced LTP in adolescent females. Combined exposure to stress and ethanol in utero reduced the ethanol-induced enhancement of LTP in females. On the other hand, exposure to stress and ethanol in utero did not alter the ethanol-induced reduction of LTP in males. These results indicate that prenatal ethanol and prenatal stress produce sex-specific alterations in synaptic plasticity in the adolescent hippocampus.

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105) ALCOHOL EXPOSURE DURING LATE GESTATION ADVERSELY AFFECTS MYOCARDIAL DEVELOPMENT WITH IMPLICATIONS FOR POSTNATAL CARDIAC FUNCTION
Goh JM, Bensley JG, Kenna K, Sozo F, Bocking AD, Brien J, Walker D, Harding R, Black MJ.
Department of Anatomy and Developmental Biology, Monash University, Clayton Campus, Bldg. 76, Victoria 3800 Australia.

ABSTRACT
Prenatal exposure to high levels of ethanol is associated with cardiac malformations, but the effects of lower levels of exposure on the heart are unclear. Our aim was to investigate the effects of daily exposure to ethanol during late gestation, when cardiomyocytes are undergoing maturation, on the developing myocardium. Pregnant ewes were infused with either ethanol (0.75 g/kg) or saline for 1 h each day from gestational days 95 to 133 (term ~145 days); tissues were collected at 134 days. In sheep, cardiomyocytes mature during late gestation as in humans. Within the left ventricle (LV), cardiomyocyte number was determined using unbiased stereology and cardiomyocyte size and nuclearity determined using confocal microscopy. Collagen deposition was quantified using image analysis. Genes relating to cardiomyocyte proliferation and apoptosis were examined using quantitative real-time PCR. Fetal plasma ethanol concentration reached 0.11 g/dL after EtOH infusions. Ethanol exposure induced significant increases in relative heart weight, relative LV wall volume, and cardiomyocyte cross-sectional area. Ethanol exposure advanced LV maturation in that the proportion of binucleated cardiomyocytes increased by 12%, and the number of mononucleated cardiomyocytes was decreased by a similar amount. Apoptotic gene expression increased in the ethanol-exposed hearts, although there were no significant differences between groups in total cardiomyocyte number or interstitial collagen. Daily exposure to a moderate dose of ethanol in late gestation accelerates the maturation of cardiomyocytes and increases cardiomyocyte and LV tissue volume in the fetal heart. These effects on cardiomyocyte growth may program for long-term cardiac vulnerability.

Read Full Article,
106) Prenatal Exposure of Ethanol Induces Increased Glutamatergic Neuronal Differentiation of Neural Progenitor Cells

Kim KC, Go HS, Bak HR, Choi CS, Choi I, Kim P, Han SH, Han SM, Shin CY, Ko KH.
Department of Pharmacology, College of Pharmacy, Seoul National University, Seoul, Korea.

ABSTRACT

Background: Prenatal ethanol exposure during pregnancy induces a spectrum of mental and physical disorders called fetal alcohol spectrum disorder (FASD). The central nervous system is the main organ influenced by FASD, and neurological symptoms include mental retardation, learning abnormalities, hyperactivity and seizure susceptibility in childhood along with the microcephaly. In this study, we examined whether ethanol exposure adversely affects the proliferation of NPC and de-regulates the normal ratio between glutamatergic and GABAergic neuronal differentiation using primary neural progenitor culture (NPC) and in vivo FASD models.

Methods: Neural progenitor cells were cultured from E14 embryo brain of Sprague-Dawley rat. Pregnant mice and rats were treated with ethanol (2 or 4 g/kg/day) diluted with normal saline from E7 to E16 for in vivo FASD animal models. Expression level of proteins was investigated by western blot analysis and immunocytochemical assays. MTT was used for cell viability. Proliferative activity of NPCs was identified by BrdU incorporation, immunocytochemistry and FACS analysis.

Results: Reduced proliferation of NPCs by ethanol was demonstrated using BrdU incorporation, immunocytochemistry and FACS analysis. In addition, ethanol induced the imbalance between glutamatergic and GABAergic neuronal differentiation via transient increase in the expression of Pax6, Ngn2 and NeuroD with concomitant decrease in the expression of Mash1. Similar pattern of expression of those transcription factors was observed using an in vivo model of FASD as well as the increased expression of PSD-95 and decreased expression of GAD67.

Conclusions: These results suggest that ethanol induces hyper-differentiation of glutamatergic neuron through Pax6 pathway, which may underlie the hyper-excitability phenotype such as hyperactivity or seizure susceptibility in FASD patients.


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107) Medical Expenditures of Children in the United States with Fetal Alcohol Syndrome

Amendah DD, Grosse SD, Bertrand J.

ABSTRACT

This paper calculates the medical expenditures for pediatric Medicaid enrollees with fetal alcohol syndrome (FAS), those with and those without reported intellectual disability (ID). The pediatric portion of the MarketScan® Medicaid Multi-State databases for the years 2003-2005 was used. Children with FAS were identified based on International Classification of Diseases, Ninth Revision, Clinical Modification codes. Children without FAS formed the comparison group. Annual mean, median, and 95(th) percentile total expenditures were calculated for those continuously enrolled during 2005. Children with FAS incurred annual mean medical expenditures that were nine times as high as those

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of children without FAS during 2005 ($16,782 vs. $1,859). ID more commonly was listed as a medical
diagnosis among children with FAS than among children in the comparison group (12% vs. 0.5%), and
mean expenditures of children with FAS and ID were 2.8 times those of children with FAS but without
reported ID. Children with FAS incurred higher medical expenditures compared with children without
FAS. A subset of children with FAS who had ID sufficiently serious to be recorded in medical records
increased those expenditures still further. Our estimate of mean expenditures for children with FAS
was several times higher than previous estimates in the United States.

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108) FASD -- DE AAR MUMS GET BEYOND THE 'TIPPLING POINT'
Bateman C.
HMPG. chrisb@hmpg.co.za.

ABSTRACT
When most of the low-income folk in the 'ghost train' town of De Aar began remonstrating with any
pregnant mother who was boozing, excited campaigners thought they'd broken through the 'tippling
point'. However, their research colleagues proved they'd gone even further -- the dedicated local
platoon of social workers, nurses, therapists and volunteers had in three short years reduced the
prevalence of fetal alcohol spectrum disorder (FASD) by 30%. This is in a town with the worst
recorded FASD prevalence in any single community in the world, where 120 out of every 1 000
residents suffer from FASD (12%).

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Public Health Agency of Canada
2nd November 2010

109) EARLY PRIMARY SCHOOL OUTCOMES ASSOCIATED WITH MATERNAL USE OF
ALCOHOL AND TOBACCO DURING PREGNANCY AND WITH EXPOSURE TO PARENT
ALCOHOL AND TOBACCO USE POSTNATALLY
Kevin Parker¹, Alison Bradshaw², Shahriar Khan², Mary Acreman¹, Ray DeV. Peters²
¹ Department of Psychology, Queen's University
² Better Beginnings, Better Futures Research Unit, Queens's University
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EXECUTIVE SUMMARY
Objective: The main purpose of the present study was to analyze longitudinal data from the "Better
Beginnings, Better Futures" (BBBF) prospective study to examine relationships between prenatal
exposure to alcohol and tobacco, separately and in combination, on developmental outcomes in
young children from disadvantaged Ontario communities over the first four years of primary school
(i.e. from 4 to 8 years of age). We also examined the effects of postnatal exposure to maternal
drinking and smoking.
Four hypotheses were explored: 1. Children with higher-risk drinking mothers would show poorer developmental outcomes than those with lower-risk drinking mothers. 2. Children whose mothers smoked during pregnancy would show poorer developmental outcomes than those whose mothers did not smoke. 3. Children whose mothers were both high-risk drinkers and smokers during pregnancy would show the greatest developmental problems during primary school. 4. Maternal drinking and smoking during pregnancy would be more predictive of children’s primary school problem behaviours than postnatal exposure to parental drinking and smoking behaviour during the preschool years.

Methodology: Two sets of statistical analyses were used. First, analysis of covariance (ANCOVA) allowed us to determine whether prenatal exposure to alcohol and/or tobacco may have differential effects on various aspects of children’s functioning during the early primary school years. This first analysis was designed as a “proof-of-concept” or exploratory model. Measures in five domains of child development outcomes were analyzed in the ANCOVA analysis: general development, cognitive development/academic performance, social/emotional functioning, behaviour problems, and physical health.

Second, based on results from the ANCOVA, a more complex statistical technique (structural equation modelling [SEM]) was used to examine the pathways from prenatal and postnatal exposure to alcohol and tobacco, to parent and teacher reports of children’s behaviour problems at age 8 (Grade 3). In this first-path analysis of this large and complex dataset, we focused on children’s externalizing (misbehaviour and problem behaviour) and internalizing (distress and emotion) behaviour problems in particular, because the latent trait structure of these behaviour problems was well enough documented in the research literature to use confirmatory techniques.

Both of the above-mentioned sets of analyses were carried out on the BBBF longitudinal dataset made up of over 400 children. These children and their families were recruited from disadvantaged Ontario communities at birth, and were followed prospectively at 33 and 48 months, and again at age 8. Thus, it was also possible to measure postnatal exposure to alcohol (i.e. maternal drinking) and tobacco (i.e. second-hand or environmental smoke), and to examine whether any negative effects of prenatal exposure to alcohol and tobacco on children’s developmental outcomes increased or decreased over a four-year period between 4 and 8 years of age. Maternal alcohol use was assessed using the CAGE questionnaire (Ewing, 1984), while maternal tobacco use was assessed with questions from the National Longitudinal Survey of Children and Youth (NLSCY) and other population surveys. For all analyses, a comprehensive set of family socioeconomic, cultural and demographic variables listed in Appendix 2 were employed as covariates in order to eliminate confounding effects of these variables.

Results: In the first ANCOVA analysis, children whose mothers reported higher-risk alcohol consumption during pregnancy showed longterm negative outcomes in measures of school performance and behaviour problems. These problems were accentuated in children whose mothers reported both alcohol and tobacco use during the pregnancy. However, negative outcomes were not evident in mothers who used only tobacco during pregnancy. Further, the negative effects were more apparent at some times than at others: when children were 4 years of age, and faced with the challenges of formal school entry (i.e. poor school readiness) and again at 8 years of age, when individual differences in conceptual thinking may have been particularly salient to teachers. The percentage of measures demonstrating the disadvantage of children exposed to prenatal alcohol and tobacco increased from 37% at age 4 to 47% at age 8. Second, results of the SEM suggest that the effects of the prenatal drinking and smoking were evident even when drinking and smoking behaviour at 33 months was taken into account. Although parental smoking behaviour (at age 33 months) predicted teacher reports of internalizing behaviour, prenatal maternal smoking accounted for both parent and teacher reports of externalizing problems and prenatal maternal drinking predicted teacher reports of both internalizing and externalizing problems.
**Conclusions:** Maternal drinking and tobacco use during pregnancy predicted that a child will have problems in elementary school, even when taking into account later smoking and drinking behaviour by the child’s parents. If these effects have endured for eight years, it seems unlikely that such effects will dissipate. If the trends are maintained as we expect, children's academic and social behaviour may continue to be compromised into early adolescence. That is, prenatal exposure to maternal drinking and smoking may be linked to problems in or negative effects associated with cognitive and social development at critical periods in children’s development, with lifelong consequences.

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J Popul Ther Clin Pharmacol Vol 17(3) Fall 2010:e405-e417; November 1, 2010

**110) TRAINING NEEDS OF HEALTHCARE PROVIDERS RELATED TO CENTERS FOR DISEASE CONTROL AND PREVENTION CORE COMPETENCIES FOR FETAL ALCOHOL SPECTRUM DISORDERS**

Christiane Brems, Rachel V Boschma-Wynn, Sarah L Dewane, Alexandra E Edwards, Rebecca V Robinson

**ABSTRACT**

**Background:** Fetal alcohol spectrum disorders (FASDs) are birth defects directly linked to consumption of alcohol during pregnancy and hence completely preventable. Many health and allied health professionals are in prime positions for primary prevention of FASDs through work with women of childbearing age and secondary prevention through work with affected individuals whose lives can be greatly improved via tailored intervention.

**Objectives:** To develop educational guidelines for FASD prevention.

**Methods:** Interviews were conducted with 26 individuals representing eight health or allied health professions. Participants were asked about professional groups with which they had sufficient experience to describe FASD-related competencies and educational needs for the given group(s). For each group, participants were asked for their perceptions of group members’ FASD awareness, knowledge, and skills application as related to the seven core competencies for FASD practice developed by the Centers for Disease Control and Prevention (CDC).

**Results:** Findings revealed that competence, especially when viewed separately in terms of knowledge versus capacity for application of information, in the area of FASDs is unevenly distributed among and throughout healthcare provider groups.

**Conclusion:** Based on this information, recommendations are offered for optimal health and allied health education efforts to prevent and treat FASDs, framed along FASD core competencies recommended by the CDC.

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http://www.cjcp.ca/pubmed.php?articleId=288

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111) EFFECT OF ALCOHOL IN COMBINATION WITH STRESS IN THE PRENATAL PERIOD ON ADULT MICE BEHAVIOUR
Morozova MV, Popova NK.

ABSTRACT
The aim of the present study was to investigate the effects of the prenatal alcohol and stress on behaviour of adult CBA/Lacj male mice. Pregnant mice were given ethanol 11% from to 21 days of the gestation and were exposed to restraint stress for two hours daily from 15 to 21 days gestation. At 3 months of age, the offspring were tested for behaviour. Alcohol and stress-exposed animals buried more marbles in the marble-burying test, which models obsessive-compulsive disorders (OCD). In addition, the alcohol and stress-exposed males showed increased social activity. No significant effects of the prenatal alcohol and stress exposure on locomotor activity, anxiety, exploring activity of the adult male mice were revealed. Conclusion was made that exposure to the alcohol and stress combination in prenatal period produces predisposition to OCD.

Link to the Article,

112) WHICH NEURODEVELOPMENTAL DISORDERS GET RESEARCHED AND WHY?
Bishop DV.
Developmental Neuropsychology, University of Oxford, Oxford, United Kingdom.
dorothy.bishop@psy.ox.ac.uk

ABSTRACT
Aim: There are substantial differences in the amount of research concerned with different disorders. This paper considers why.

Methods: Bibliographic searches were conducted to identify publications (1985-2009) concerned with 35 neurodevelopmental disorders: Developmental dyslexia, Developmental dyscalculia, Developmental coordination disorder, Speech sound disorder, Specific language impairment, Attention deficit hyperactivity disorder, Autistic spectrum disorder, Tourette syndrome, Intellectual disability, Angelman syndrome, Cerebral palsy, Cornelia de Lange syndrome, Cri du chat syndrome, Down syndrome, Duchenne muscular dystrophy, Fetal alcohol syndrome, Fragile X syndrome, Galactosaemia, Klinefelter syndrome, Lesch-Nyhan syndrome, Lowe syndrome, Marfan syndrome, Neurofibromatosis type 1, Noonan syndrome, Phenylketonuria, Prader-Willi syndrome, Rett syndrome, Rubinstein-Taybi syndrome, Trisomy 18, Tuberous sclerosis, Turner syndrome, Velocardiofacial syndrome, Williams syndrome, XXX and XYY. A publication index reflecting N publications relative to prevalence was derived.

Results: The publication index was higher for rare than common conditions. However, this was partly explained by the tendency for rare disorders to be more severe.

Interpretation: Although research activity is predictable from severity and prevalence, there are exceptions. Low rates of research, and relatively low levels of NIH funding, characterise conditions that are the domain of a single discipline with limited research resources. Growth in research is not
explained by severity, and was exceptionally steep for autism and ADHD.

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113) INVESTIGATING THE EFFICACY OF AN ATTENTION TRAINING PROGRAMME IN CHILDREN WITH FOETAL ALCOHOL SPECTRUM DISORDER
Kerns KA, Macsween J, Vander Wekken S, Gruppuso V.  
Psychology, University of Victoria, Victoria, British Columbia, Canada. kkerns@uvic.ca

ABSTRACT  
Objective: The current study investigated the efficacy of a direct intervention programme aimed at improving attention abilities in children with foetal alcohol spectrum disorder (FASD).

Methods: The Computerized Progressive Attention Training (CPAT) program is an intervention which targets proposed attention networks. CPAT task difficulty automatically adjusts based on participant performance. Ten children aged 6-15 with FASD completed an average of 16 hours of intervention over ~9 weeks at school, aided by a research assistant providing metacognitive strategies and support.

Results: Pre- and post-intervention assessments indicate significant improvement on several attention measures including sustained attention and selective attention. In addition, several measures of spatial working memory, math fluency, and reading fluency also significantly increased, suggesting that better attention leads to better cognitive performance.

Conclusion: Results provide support for the use of computerized attention training materials as part of an effective intervention for cognitive performance in children with FASD.

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114) ABNORMAL BRAIN ACTIVATION DURING WORKING MEMORY IN CHILDREN WITH PRENATAL EXPOSURE TO DRUGS OF ABUSE: THE EFFECTS OF METHAMPHETAMINE, ALCOHOL, AND POLYDRUG EXPOSURE
Roussotte FF, Bramen JE, Nunez SC, Quandt LC, Smith L, O'Connor MJ, Bookheimer SY, Sowell ER.  
Department of Neurology, David Geffen School of Medicine at UCLA, University of California, Los Angeles, CA 90095-7332, USA. florence78@ucla.edu

ABSTRACT  
Structural and metabolic abnormalities in fronto-striatal structures have been reported in children with prenatal methamphetamine (MA) exposure. The current study was designed to quantify functional alterations to the fronto-striatal circuit in children with prenatal MA exposure using functional magnetic resonance imaging (fMRI). Because many women who use MA during pregnancy also use alcohol, a
known teratogen, we examined 50 children (age range 7-15), 19 with prenatal MA exposure, 15 of whom had concomitant prenatal alcohol exposure (the MAA group), 13 with heavy prenatal alcohol but no MA exposure (ALC group), and 18 unexposed controls (CON group). We hypothesized that MA exposed children would demonstrate abnormal brain activation during a visuospatial working memory (WM) "N-Back" task. As predicted, the MAA group showed less activation than the CON group in many brain areas, including the striatum and frontal lobe in the left hemisphere. The ALC group showed less activation than the MAA group in several regions, including the right striatum. We found an inverse correlation between performance and activity in the striatum in both the CON and MAA groups. However, this relationship was significant in the caudate of the CON group but not the MAA group, and in the putamen of the MAA group but not the CON group. These findings suggest that structural damage in the fronto-striatal circuit after prenatal MA exposure leads to decreased recruitment of this circuit during a WM challenge, and raise the possibility that a rewiring of cortico-striatal networks may occur in children with prenatal MA exposure.

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115) EFFECTS OF PRENATAL ETHANOL EXPOSURE ON THE LUNGS OF POSTNATAL LAMBS  
Dept. of Anatomy and Developmental Biology, Monash Univ., VIC, Australia.

ABSTRACT
Prenatal ethanol exposure increases collagen deposition and alters surfactant protein (SP) expression and immune status in lungs of near-term fetal sheep. Our objectives were to determine 1) whether these prenatal effects of repeated gestational ethanol exposure persist after birth and 2) whether surfactant phospholipid composition is altered following prenatal ethanol exposure. Pregnant ewes were chronically catheterized at 90 days of gestational age (DGA) and given a 1-h daily infusion of ethanol (0.75 g/kg, n = 9) or saline (n = 7) from 95 to 135 DGA; ethanol administration ceased after 135 DGA. Lambs were born naturally at full term (146 ± 0.5 DGA). Lung tissue was examined at 9 wk postnatal age for alterations in structure, SP expression, and inflammation; bronchoalveolar lavage fluid was examined for alterations in surfactant phospholipid composition. At 134 DGA, surfactant phospholipid concentration in amniotic fluid was significantly reduced (P < 0.05) by ethanol exposure, and the composition was altered. In postnatal lambs, there were no significant differences between treatment groups in birth weight, postnatal growth, blood gas parameters, and lung weight, volume, tissue fraction, mean linear intercept, collagen content, proinflammatory cytokine gene expression, and bronchoalveolar lavage fluid surfactant phospholipid composition. Although SP-A, SP-B, and SP-C mRNA levels were not significantly different between treatment groups, SP-D mRNA levels were significantly greater (P < 0.05) in ethanol-treated animals; as SP-D has immunomodulatory roles, innate immunity may be altered. The adverse effects of daily ethanol exposure during late gestation on the fetal lung do not persist to 2 mo after birth, indicating that the developing lung is capable of repair.

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J Popul Ther Clin Pharmacol Vol 17 (3) Fall 2010:e390-e404; October 26, 2010
116) ROLE OF CENTRAL NERVOUS SYSTEM INSULIN RESISTANCE IN FETAL ALCOHOL SPECTRUM DISORDERS
Suzanne M de la Monte, Jack R Wands

ABSTRACT
Fetal alcohol spectrum disorder (FASD) is the most common preventable cause of mental retardation in the USA. Ethanol impairs neuronal survival and function by two major mechanisms: 1) it inhibits insulin signaling required for viability, metabolism, synapse formation, and acetylcholine production; and 2) it functions as a neurotoxicant, causing oxidative stress, DNA damage and mitochondrial dysfunction. Ethanol inhibition of insulin signaling is mediated at the insulin receptor (IR) level and caused by both impaired receptor binding and increased activation of phosphatases that reverse IR tyrosine kinase activity. As a result, insulin activation of PI3K-Akt, which mediates neuronal survival, motility, energy metabolism, and plasticity, is impaired. The neurotoxicant effects of ethanol promote DNA damage, which could contribute to mitochondrial dysfunction and oxidative stress. Therefore, chronic in utero ethanol exposure produces a dual state of CNS insulin resistance and oxidative stress, which we postulate plays a major role in ethanol neurobehavioral teratogenesis. We propose that many of the prominent adverse effects of chronic prenatal exposure to ethanol on CNS development and function may be prevented or reduced by treatment with peroxisome-proliferated activated receptor (PPAR) agonists which enhance insulin sensitivity by increasing expression and function of insulin-responsive genes, and reducing cellular oxidative stress.

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117) THE EFFECTS OF MATERNAL BINGE DRINKING DURING PREGNANCY ON NEURAL CORRELATES OF RESPONSE INHIBITION AND MEMORY IN CHILDHOOD
Burden MJ, Westerlund A, Muckle G, Dodge N, Dewailly E, Nelson CA, Jacobson SW, Jacobson JL. Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, Michigan 48207, USA.

ABSTRACT
Background: Although an extensive literature has documented a broad range of cognitive performance deficits in children with prenatal alcohol exposure, little is known about how the neurophysiological processes underlying these deficits may be affected. Event-related potentials (ERPs), which reflect task-specific changes in brain electrical activity, provide a method for examining multiple constituents of cognitive processing at the neural level.

Methods: We recorded ERPs in 217 children from Inuit communities in Arctic Quebec (M age = 11.3 years) during 2 different tasks-Go/No-go response inhibition and continuous recognition memory. Children were classified as either alcohol-exposed (ALC) or controls (CON) depending on whether the mother reported binge drinking during pregnancy.

Results: Both groups performed comparably in terms of accuracy and reaction time on the tasks, and both tasks elicited the expected effects on ERPs when responses were compared across conditions. However, the ALC group showed slower P2 latencies on Go/No-go, suggesting an altered neurophysiological response associated with initial visual processing of the stimuli. On the memory
task, the ALC group showed reduced FN400 amplitude to New items, known as the familiarity effect, and reduced amplitude for the late positive component, possibly reflecting impairment in memory retrieval.

**Conclusions**: These findings show that, even in tasks in which alcohol-exposed children exhibit behavioral performance that is comparable to controls, fetal alcohol exposure is associated with altered neurophysiological processing of response inhibition and recognition memory. The data suggest that fetal alcohol exposure is associated with reduced efficiency in the initial extracting of the meaning of a stimulus, reduced allocation of attention to the task, and poorer conscious, explicit recognition memory processing.

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behavioral effects of ethanol, especially the enhanced ethanol intake known to occur after moderate ethanol prenatally or during nursing, depend upon teratological effects that may include death of neurons in the main olfactory bulb (MOB). During gestational days 17-20 rats were given 0, 1 or 2g/kg ethanol doses intragastrically (i.g.). After parturition these dams were given a dose of 2.5g/kg ethanol i.g. each day and allowed to perform regular nursing activities. During postnatal days (PDs) 15 and 16, ethanol intake of pups was assessed along with aspects of their general activity. In a second experiment pups given the same prenatal treatment as above were tested for blood ethanol concentration (BEC) in response to an ethanol challenge on PD6. A third experiment (Experiment 2b) assessed stereologically the number of cells in the granular cell layer of the MOB on PD7, as a function of analogous pre- and postnatal ethanol exposures. Results revealed that ethanol intake during the third postnatal week was increased by prenatal as well as postnatal ethanol exposure, with a few interesting qualifications. For instance, pups given 1g/kg prenatally did not have increased ethanol intake unless they also had experienced ethanol during nursing. There were no effects of ethanol on either BECs or conventional teratology (cell number). This increases the viability of an explanation of the effects of prenatal and early postnatal ethanol on later ethanol intake in terms of learning and memory.

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120) DEVELOPMENTAL MALFORMATION OF THE CORPUS CALLOSUM: A REVIEW OF TYPICAL CALLOSAL DEVELOPMENT AND EXAMPLES OF DEVELOPMENTAL DISORDERS WITH CALLOSAL INVOLVEMENT
Paul LK.
Division of Humanities and Social Sciences, California Institute of Technology, HSS 228-77, Caltech, Pasadena, CA, 91125, USA, lkpaul@hss.caltech.edu.

ABSTRACT
This review provides an overview of the involvement of the corpus callosum (CC) in a variety of developmental disorders that are currently defined exclusively by genetics, developmental insult, and/or behavior. I begin with a general review of CC development, connectivity, and function, followed by discussion of the research methods typically utilized to study the callosum. The bulk of the review concentrates on specific developmental disorders, beginning with agenesis of the corpus callosum (AgCC)-the only condition diagnosed exclusively by callosal anatomy. This is followed by a review of several genetic disorders that commonly result in social impairments and/or psychopathology similar to AgCC (neurofibromatosis-1, Turner syndrome, 22q11.2 deletion syndrome, Williams syndrome, and fragile X) and two forms of prenatal injury (premature birth, fetal alcohol syndrome) known to impact callosal development. Finally, I examine callosal involvement in several common developmental disorders defined exclusively by behavioral patterns (developmental language delay, dyslexia, attention-deficit hyperactive disorder, autism spectrum disorders, and Tourette syndrome).

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ABSTRACT

Objective: to establish national standards of care for the screening and recording of alcohol use and counselling on alcohol use of women of child-bearing age and pregnant women based on the most up-to-date evidence.

Evidence: published literature was retrieved through searches of PubMed, CINAHL, and the Cochrane Library in May 2009 using appropriate controlled vocabulary (e.g., pregnancy complications, alcohol drinking, prenatal care) and key words (e.g., pregnancy, alcohol consumption, risk reduction). Results were restricted to literature published in the last five years with the following research designs: systematic reviews, randomized control trials/controlled clinical trials, and observational studies. There were no language restrictions. Searches were updated on a regular basis and incorporated in the guideline to May 2010. Grey (unpublished) literature was identified through searching the websites of health technology assessment (HTA) and HTA-related agencies, national and international medical specialty societies, clinical practice guideline collections, and clinical trial registries. Each article was screened for relevance and the full text acquired if determined to be relevant. The evidence obtained was reviewed and evaluated by the members of the Expert Workgroup established by the Society of Obstetricians and Gynaecologists of Canada. The quality of evidence was evaluated and recommendations were made according to guidelines developed by the Canadian Task Force on Preventive Health Care.

Values: the quality of evidence was rated using the criteria described by the Canadian Task Force on Preventive Health Care (Table 1).

Sponsor: the Public Health Agency of Canada and the Society of Obstetricians and Gynaecologists of Canada. ENDORSEMENT: these consensus guidelines have been endorsed by the Association of Obstetricians and Gynecologists of Quebec; the Canadian Association of Midwives; the Canadian Association of Perinatal, Women's Health and Neonatal Nurses (CAPWHN); the College of Family Physicians of Canada; the Federation of Medical Women of Canada; the Society of Rural Physicians of Canada; and Motherisk. SUMMARY STATEMENTS: 1. There is evidence that alcohol consumption in pregnancy can cause fetal harm. (II-2) There is insufficient evidence regarding fetal safety or harm at low levels of alcohol consumption in pregnancy. (III) 2. There is insufficient evidence to define any threshold for low-level drinking in pregnancy. (III) 3. Abstinence is the prudent choice for a woman who is or might become pregnant. (III) 4. Intensive culture-, gender-, and family-appropriate interventions need to be available and accessible for women with problematic drinking and/or alcohol dependence. (II-2).

Recommendations: 1. Universal screening for alcohol consumption should be done periodically for all pregnant women and women of child-bearing age. Ideally, at-risk drinking could be identified before pregnancy, allowing for change. (II-2B) 2. Health care providers should create a safe environment for women to report alcohol consumption. (III-A) 3. The public should be informed that alcohol screening and support for women at risk is part of routine women's health care. (III-A) 4. Health care providers should be aware of the risk factors associated with alcohol use in women of reproductive age. (III-B) 5. Brief interventions are effective and should be provided by health care providers for women with at-risk drinking. (II-2B) 6. If a woman continues to use alcohol during pregnancy, harm reduction/treatment strategies should be encouraged. (II-2B) 7. Pregnant women should be given priority access to withdrawal management and treatment. (III-A) 8. Health care providers should advise women that low-level consumption of alcohol in early pregnancy is not an indication for
termination of pregnancy. (II-2A).

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122) PRENATAL ALCOHOL EXPOSURE AS AN ETIOLOGICAL FACTOR IN NEUROPSYCHIATRIC DISEASES OF CHILDHOOD, ADOLESCENCE AND ADULTHOOD
Evrard SG.
Hospital Neuropsiquiátrico Braulio A. Moyano, Instituto de Biología Celular y Neurociencias Prof. Eduardo De Robertis, Facultad de Medicina, Universidad de Buenos Aires. sgevrard@yahoo.com.ar

ABSTRACT
In Argentina, prenatal alcohol exposure (PAE) is an almost neglected condition as an important etiological factor for the induction of a wide spectrum of neuropsychiatric diseases that may appear during childhood, adolescence or adulthood. Children born to alcoholic mothers may show a spectrum of diseases ranging from an apparent normality to a profound mental retardation, passing through epilepsy, attention deficit disorders with or without hyperactivity, autism and pervasive developmental disorders, and different types of learning disorders. When adolescents, they may develop different kinds of personality disorders and substance abuse disorders. Finally, in adulthood, they may suffer from different types of affective and psychotic disorders, among others. A great number of those children may not develop their full mental and social potentiality as free individuals. They usually have diverse types of cognitive, attentional, mnemonic and affective impairments. Not infrequently, they engage in antisocial behaviors, have school or work troubles. In this work, I review the present clinical classifications of the disorders emerging from a PAE and the several neuropsychiatric diseases that can be induced by them, in order to call attention to the Argentinian neuropsychiatric community about the increasingly, although underdiagnosed, frequency of these disorders in our country.

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123) A FRAMEWORK FOR 3D ANALYSIS OF FACIAL MORPHOLOGY IN FETAL ALCOHOL SYNDROME

ABSTRACT
Surface-based morphometry (SBM) is widely used in biomedical imaging and other domains to localize shape changes related to different conditions. This paper presents a computational framework that integrates a set of effective surface registration and analysis methods to form a unified SBM processing pipeline. Surface registration includes two parts: surface alignment in the object space by employing the iterative closest point (ICP) method, and surface alignment in the parameter space by using conformal mapping and landmark-based thin-plate spline methods. Statistical group analysis of registered surface data is then conducted by surface-based general linear model and random field

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theory addressing multiple testing issues. The effectiveness of the proposed framework is demonstrated by applying it to a fetal alcohol syndrome (FAS) study for identifying facial dysmorphology in FAS patients.

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124) PRENATAL STRESS AND ETHANOL EXPOSURE PRODUCES INVERSION OF SEXUAL PARTNER PREFERENCE IN MICE
Popova NK, Morozova MV, Amstislavskaya TG.
Laboratory of Behavioral Neurogenomics, Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Lavrentyev Avenue, 10, 630090 Novosibirsk, Russia.

ABSTRACT
The presence of a sexually receptive female behind perforated transparent partition induced sexual arousal and specific behavior in male mice so they spent more time near partition in an attempt to make their way to the female. Three-chambered free-choice model was used to evaluate sexual partner preference. The main pattern of sexual preference was the time spent by a male mouse at the partition dividing female (F-partition time) versus a partition dividing male (M-partition time). Pregnant mice were given ethanol (11vol.%) for 1-21 gestational days, and were exposed to restraint stress (2h daily for 15-21 day of the gestation). Control pregnant mice had free access to water and food and were not stressed. Adult male offspring of ethanol and stress exposed dams (E+S) showed decreased F-partition time and increased M-partition time. Whereas F-partition time in all control mice prevailed over M-partition time, 78% E+S mice demonstrated prevailed M-partition time. E+S mice were more active in social interaction with juvenile male. No significant differences between E+S and control mice in the open field and novelty tests were revealed. Therefore, E+S exposure during dam gestation inverted sexual partner preference in male offspring, suggesting that stress and alcohol in pregnancy produces predisposition to homosexuality.

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125) EVALUATION OF A SERVICE PROVIDER SHORT COURSE FOR PREVENTION OF FETAL ALCOHOL SYNDROME (FAS)
J Mwansa-Kambawile, L London, K Rendall-Mkosi, N Morojele, R.Jacobs, E Nel

Department of Public Health and Family Medicine, University of Cape Town, School of Health Systems and Public Health, University of Pretoria, Medical Research Council

ABSTRACT
Background: South Africa has among the highest reported rates of Fetal Alcohol Syndrome (FAS) globally. Primary prevention targeting women at risk of alcohol-exposed pregnancies (AEP) could substantially reduce the incidence of FAS. We evaluated the effectiveness of a short training intervention to improve service providers’ screening, identification and management of women at risk of AEPs.
Methods: Training to screen and counsel women at risk for AEPs was offered to service providers in two municipalities in the Western Cape Province, South Africa. Effectiveness was evaluated through a before-after study of service providers' knowledge and confidence levels and a comparison of service providers' practices (assessed indirectly via service user exit interviews) at intervention and control clinics.

Result: The proportion of service providers indicating alcohol during pregnancy as harmful to the fetus increased after training (23% vs 67%; p < 0.001). After training, providers expressed significantly more confidence for 4 skills indicators related to the identification and management of women at risk for AEP. Female clients at intervention clinics were more likely than those at the control clinics to receive alcohol advice (OR=2.13; 95% CI:1.27 to 3.53), counselling (OR=1.3; CI=1.05 to 1.56) and an offer of family planning (OR=1.1; CI=1.06 to 2.10) after the training. Time-group interaction variable analysis in multiple logistic regression modelling confirmed these effects as related to training.

Conclusion: A short training course, based on brief motivational interviewing principles, appears to be effective in building service provider capacity to better prevent and manage women at risk of AEPs.

126) WHICH METHOD OF SURVEILLANCE WOULD ASSIST IN THE PREVENTION OF FETAL ALCOHOL SYNDROME?
Neo Morojele, Kirstie Rendall-Mkosi, Leslie London
School of Health Systems and Public Health, University of Pretoria, Alcohol and Drug Research Unit, Medical Research Council, School of Public Health and Family Medicine, University of Cape Town,
Email: neo.morojele@mrc.ac.za

ABSTRACT
Background: Fetal Alcohol Syndrome (FAS) is of major concern in various parts of South Africa, and one of the most preventable birth defects affecting children worldwide. It is desirable that epidemiological data is available for common birth defects and conditions, especially those that can be prevented, such as FAS in South Africa. Preventive interventions as well as rehabilitative and support services could be better planned and implemented if the prevalence of FAS and the risk for FAS were known for all areas. Despite the extremely high rates of FAS in some areas of South Africa, and the recognition by some provinces of FASD as priority health and social issue, there is no national registry or surveillance system in place. Some surveys of primary schools children for FAS have been conducted in different regions in order to establish the prevalence of FAS and the factors associated with FAS. Despite its merits, this method is very expensive, logistically demanding and has various ethical dilemmas related to case finding where there are no support services available. Another method of estimating the FAS rate is to determine the prevalence of women at highest risk of an alcohol-exposed pregnancy (AEP) based on population based surveys of childbearing age women.

Methods: A survey was conducted among women of child-bearing age in a rural and urban location in South Africa.

Results: The rural women (8.5%) were more likely than their urban counterparts (2.48%) to be at risk of an AEP. These obtained rates of risk of alcohol-exposed pregnancies were similar to the rates of FAS obtained for similar rural and urban locations in South Africa.

Conclusion: Surveys of women could be a cost-effective and more ethically acceptable method of providing much needed epidemiological data at the population level.
127) RESTRICTION OF ALCOHOL CONSUMPTION AMONG PREGNANT MOTHERS: A NECESSARY STEP IN MATERNAL AND INFANT HEALTH
Kazibwe Andrew
College of Health Sciences, Makerere University, Kampala
Email: kazibweandy@yahoo.co.uk

ABSTRACT
Background: Research reveals that maternal alcohol consumption during pregnancy poses serious health risks to the unborn child. These include neurological and behavioural developmental disorders; some of the major characteristics of Fetal Alcohol Syndrome (FAS), including low birth weight; preterm birth, miscarriages and others. This has been used as the basis for advising pregnant women to reduce alcohol consumption or completely abstain from it during pregnancy for the better health of their children. There is no clear definition of how low is safe enough for the baby. Little has been discussed about the increased risk of maternal mortality created by maternal alcohol consumption during pregnancy.

Methods: A review of online literature was done to establish arguments for and against restriction of maternal alcohol consumption during pregnancy; the various causes of maternal mortality and possible association with maternal alcohol consumption.

Results: FAS is the leading preventable cause of mental retardation. There is no clear limit on the amount of alcohol that is safe for the baby at any one time during pregnancy. Maternal alcohol consumption has been found to be associated with some of the leading causes of maternal mortality including teenage pregnancy, prolonged vaginal bleeding, placenta abruptio and placenta praevia, pre-eclampsia and eclampsia; and poor infant health!

Conclusions and Recommendations: Maternal alcohol consumption could be playing a significant role in the high maternal mortality rates in Uganda. Mothers should be equipped with information regarding the dangers of maternal alcohol consumption during pregnancy to enable them to make informed decisions. More research should be done to investigate the role of alcohol as a contributing factor to a maternal mortality.

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128) CHILDHOOD BEHAVIORAL AND DEVELOPMENTAL DISORDERS: ASSOCIATION WITH MATERNAL ALCOHOL CONSUMPTION AND USE OF HEALTH SERVICES IN CAPE TOWN, SOUTH AFRICA
Elizabeth Katwan, Leslie London, Colleen Adnams

ABSTRACT
Objectives: We examined the association of childhood behavioural and developmental disorders (BDD) with maternal alcohol consumption and with health fertility utilization.

Methods: Parents or caretakers of 55 children ages 4 to 12 years with BDD and 55 controls of similar age were interviewed at a tertiary public children’s hospital in Cape Town, South Africa. Logistic regression was used to compare maternal alcohol consumption and health service utilization between groups.

Results: BDD were significantly associated with current maternal alcohol consumption (Adjusted Odds Ratio (AOR)=2.98; 95% Confidence Interval (CI)=1.02, 8.70), maternal binge drinking in the last six months (AOR=4.67; 95% CI=1.10, 19.90), and maternal alcohol use six months before pregnancy (AOR=3.00; 95% CI=1.12, 8.03), but no significantly with reported maternal gestational drinking
(AOR=1.77; 95% CI=0.57, 5.53). The median number of visits to a clinic in the last six months was significantly higher for cases than for controls (6 versus 2; p<0.001).

**Conclusions:** Current maternal alcohol consumption, a possible proxy for unstable home environments, is significantly associated with childhood BDD. An effect from gestational alcohol consumption could not be conclusively demonstrated in our data.

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**129) THE ALCOHOL AND TOBACCO INFORMATION GIVEN TO URUGUAY PREGNANT MOTHERS BY THE HEALTH TEAM**

Magri R., Suarez M., Miguez H., Suares H

**ABSTRACT**

**Introduction:** In Uruguay there is still not enough work with women’s group related to prevention/information of alcohol or tobacco, although Uruguay has being working against tobacco use since 2006 when a law banned the use of tobacco in any form in all public places. During 2005, 2007 and 2009 our research group studied the prevalence of alcohol, tobacco and other drugs consumption of Uruguay pregnant women during their pregnancy with surveys and biomarkers. In all three studies prevalence of alcohol use assessed by survey was over 37.7% and tobacco use over 38.8%. Data from biomarkers were higher than the survey estimates.

In relation to other countries and pregnant women of the same SES those data are considered high. Among other variables, we explored the information the health team gives to pregnant women in Uruguay.

**Methods:** A survey of a convenience sample of 250 postpartum women was conducted between 05/07/09 and 06/20/09. The questionnaire, which had received ethical approval, was confidential, obtained informed consent, and included both open-ended and pre-coded questions.

**Results:** Information on alcohol: No information was provided to 66.5% of the women; 33.5% received some type of information. Among those women who did receive some information, the health team gave the following information: drinking might harm the baby (48.7%); drinking might diminish the BB reflexes (4.8%); the mother was HT (1.2%); they should not drink (32.9%); they should drink less (4.9%). 10.9% of the women did not remember the information given. There was no specification on SFA.

Information on tobacco: No information was provided to 58% of the women; some information was provided to 42%. Among those who did receive some information, the health team said the following: they should not smoke (29.1%); they should smoke less (5.8%); smoking might produce ISD (2.9%); smoking is ‘bad’ for the baby (reason not specified) (13.6%); smoking might cause the baby to have heart or respiratory problems, be smaller or have other problems (66.9%).

**Conclusions:** Considering that more than 1/3 of the women in this sample consumed alcohol and used tobacco during their pregnancy, there is a low and incomplete level of information. Strategies for these specific populations (mothers and health teams) should be planned (who, how and what should be said) related to alcohol and tobacco consumption during, before and after pregnancy.

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B. ALCOHOL FREE MOUTHWASH SIGNIFICANTLY REDUCED PRETERM BIRTHS IN STUDY

Researchers say pregnant women who focus on periodontal health during pregnancy with alcohol free antibacterial mouthwash have lower chances of preterm birth. The findings are presented February 11 at the Society for Maternal-Fetal Medicine's (SMFM) annual meeting.

The researchers say their findings are "exciting", that something as simple as using mouthwash containing cetylpyridinium chloride (CPC) could prevent preterm birth that causes significant morbidity and mortality worldwide.

The study was funded by Commonwealth of Pennsylvania and The Procter & Gamble Company that was a controlled blind clinical study of pregnant women at 6-20 weeks gestation who had periodontal disease but refused dental treatment.

The number of women enrolled was 204. One group was used as a control and included 155 participants. A group of 49 women received the non-alcohol antibacterial, Crest Pro-Health, mouthwash. All of the women were questioned about prior preterm birth and smoking history.

Baseline dental exams were performed and again just before delivery. The primary outcome of the study was preterm delivery before 35 weeks gestation.

According to Marjorie Jeffcoat, D.M.D., one of the study's authors, "Preterm birth is the major cause of perinatal mortality and morbidity worldwide and still difficult to predict and prevent. This research demonstrated that reducing the severity of periodontal disease has a direct correlation with preterm birth."

The group of women given the mouthwash had significantly lower rates of preterm birth. The researchers also note the women were older than the control group and had infants with higher birth weight and gestational age.

Link to the Article,
http://www.examiner.com/women-s-health-in-national/alcohol-free-mouthwash-significantly-reduced-preterm-births-study#ixzz1LO2kZLpu

C. FISH RAISED IN ALCOHOL MAY PROVIDE CLUES TO HUMAN DRINKING PROBLEMS

Can slightly drunk fish help scientists learn how to treat alcoholism in humans? Robert Gerlai, a professor at the University of Toronto's Mississauga campus, thinks they can.

Gerlai, who holds a PhD in biology, specializing in behavioural genetics, said little zebra fish grown from eggs in water laced with ethyl alcohol could even hold secrets to treating children with fetal
alcohol syndrome.

―The ultimate goal is to understand how alcohol alters brain function in vertebrates (including humans) which will eventually lead to a better understanding of alcoholism, alcohol abuse, all kinds of problems and perhaps better treatment, eventually," he said.

―Because once you understand the neurological and biological mechanisms of alcohol abuse, you can target particular molecular pathways and biochemical mechanisms and develop pills or other treatment solutions.‖

It’s a roundabout way of saying that some fish show similar reactions to alcohol and may point to solutions in humans.

―We gave small amounts of alcohol to tiny, tiny eggs, 24 hours after fertilization, when the embryo has just started to develop," Gerlai said. He said the amount of alcohol ―doesn’t lead to any major anatomy change‖ in the fish.

―So these fish grow well, they develop seemingly normally; they reach adulthood and look absolutely fine. But when we give these fish behavioural tests, they become anti-social.‖

That is abnormal, because zebra fish are highly social and form groups much more tightly than other fish. Zebra fish usually clump together. The groups aren’t as tight in fish that receive alcohol, he said.

―In fish, the loosening to the group is dose dependent," Gerlai said. ―The more alcohol we give them, the more anti-social they become as adults.

―It changed their social skills, which resemble what you find in mild fetal alcohol syndrome in humans.‖

In the end, Gerlai hopes his research leads to better treatment for alcohol-related problems.

―Imagine that you have a fish that mimics many aspects of fetal alcohol syndrome," he said. ―You can look at the brain, the anatomy, how cells in the brain work and whether there any modifications of their ability to communicate with each other.

―We have the ability to investigate a lot of neurobiological questions that normally you would not be able to do with humans.‖

Gerlai and Luis Gomez-Laplaza, of the University of Oviedo in Spain, recently completed another study that shows angelfish are able to estimate the size of groups and count up to three of their swimming buddies.

Their study found that angelfish had the ability to choose between groups of other angelfish of varying
They do not count the fish, they do not actually perform mathematical calculations," he explained. What they probably do is estimate the size of the group based on some quantitative characteristic of the group.

"We don't know exactly what it is."

**Link to the Article,**

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**StarTribune, St Paul – 24th January 2011**
**Article by Jeremy Olson**

**D. MAJOR HEALTH STUDY WILL TRACK CHILDREN FROM PRE-BIRTH TO 21**

Four decades ago, a massive study of American children helped unlock discoveries about secondhand smoke, sudden infant death syndrome and fetal alcohol syndrome.

Now researchers want to repeat that approach, and they are starting to recruit expectant mothers in Ramsey County as one of 105 sites in an ambitious national study of children and families. The study will last for decades and examine the genetic, environmental and social determinants of childhood health and disease.

"Times have changed since the early '60s," said Pat McGovern, a University of Minnesota professor who will be lead researcher of the Minnesota arm of the study. "We have more single-parent families [and] more two-parent families in which both parents are working. Immigration patterns have changed. Children's exercise and diet habits have changed. There's a whole lot more chemicals we're all exposed to in the air and water."

Overall, the federally funded National Children's Study aims to follow 100,000 children from before birth until age 21. Study leaders selected counties on the basis of their diversity, birth rates and rates of childhood health problems such as asthma. Ramsey County offered a unique mix of urban and suburban neighborhoods, along with a large Hmong community.

A kickoff event for the study will take place Monday in St. Paul. Study promotions will include a tent at the upcoming St. Paul Winter Carnival.

The University of Minnesota will seek 100 to 300 women from 16 neighborhoods this year for a startup phase of the study. The areas range from St. Paul's Highland and Frogtown neighborhoods to Arden Hills and White Bear Lake. Another 1,000 women who are pregnant or planning to become pregnant will be enrolled two to three years later.

"What we learn ... could lead to new treatments and preventive practices for all sorts of health concerns we have as parents and as health care providers," McGovern said. "We are never going to be able to effectively prevent childhood health conditions until we fully understand what contributes to them."

Parents have been shocked at the length of the study, said Catherine Graeve, a St. Paul mother of
three who is promoting it. She nonetheless expects many to enroll, given parents' heightened curiosity these days about everything from plastic in water bottles to whey in bread.

"Right now, it's trendy to want to know those things about your kids," said Graeve, 31. "So I feel like this is good timing. Moms, parents, they want to know what's going to keep their kids healthy."

Ramsey County's selection for the study was announced three years ago. Delays and a change in federal administration pushed back the start, McGovern said. Three western Minnesota counties are part of a South Dakota arm of the study. Three northern Minnesota counties with high American Indian populations were considered, but at this point aren't being included.

Researchers expect results to trickle out as the children age. Initial studies are likely to examine the demographics and environments of women who give birth preterm. As participating children grow, studies will emerge on their varying levels of asthma, autism and other conditions.

"I'm thinking about those major health risk factors that continue to kind of grow out of proportion, like asthma and autism and obesity," said Mary Sue Hansen, who is studying local causes of health problems through the Suburban Ramsey Family Collaborative. "I continue to think there are environmental factors. We just haven't figured out what they are."

Some results from the National Children's Study might not come for decades.

"We hope the families will feel a point of pride that they're contributing to the national knowledge base on childhood health and development," McGovern said. "It will be their children's children and the next generation [that will benefit]. So it's really a legacy moving forward."

Link to the Article,
http://www.startribune.com/local/stpaul/114461489.html

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E. U.K. BOOZE STUDY 'SET US BACK YEARS'

[Headnote]
Canadian FASD expert decries research sanctioning alcohol use during pregnancy

MAPLE RIDGE, B.C. A recent U.K. study suggesting women can consume small amounts of alcohol during pregnancy has "set us back years" in the fight against fetal alcohol spectrum disorder (FASD), says a prominent expert in the field.

Dr. Kwadwo Asante, founder and medical director of the Asante Centre for Fetal Alcohol Syndrome here, said in the absence of definitive evidence that engaging in light drinking does not harm the fetus, pregnant women should avoid alcohol consumption altogether.

"We know that alcohol causes problems, but we don't know exactly where the threshold amount is. Is it one (drink) a week? Two a week? Or is it that if you drink during early pregnancy your child is home free after that? We don't know," he said in an interview.

The study - led by Dr. Yvonne KeUy (PhD) of University College London and published online in October by the Journal of Epidemiology and Community Health-showed that children born to women
who had one or two alcoholic drinks a week during pregnancy were not at increased risk for
behavioural dysfunction or cognitive deficit at age five years, compared with children of nondrinkers,
and in fact performed better on some cognitive tests.

"For someone to say children whose mothers had two to six drinks a week performed better than
those whose mothers did not drink does not make sense," Dr. Asante said.

He noted the study was seriously flawed because it relied on face-to-face interviews with mothers of
children born between 2000 and 2002. In these types of studies, interviewees commonly misreport the
amount of alcohol consumed during pregnancy, he said. The study also failed to examine physical
characteristics associated with FASD.

"There are various malformations in the kidneys and in the brain, and more frequently physical signs in
the heart and face that indicate FASD. The study restricted itself to behaviour and developmental
things."

In addition to undergoing standard physical measurements including birth weight, length and head
circumference, children should be tracked well into their teen years, when FASD can manifest in
serious behavioural problems, Dr. Asante said. The U.K. study "fell short of that" by tracking children
up to only five years of age.

Dr. Asante said most doctors are aware of FASD, but "it's not on the radar" in their actual practices.
When physicians do suspect FASD, they need to look for three physical characteristics of the
condition: a shorter-than-normal palpebral fissure, a flattened philtrum and a thin upper lip.

Dr. Asante stressed these and other abnormalities, including heart murmur, should be considered in
conjunction with one another. And while a child may have no immediate symptoms, a knowledgeable
physician who feels a child is a bit small or is not growing well should try to learn more about the
pregnancy and the mother's history. "It's not just about measuring the child's weight or length - you
look at the child as a whole."

Dr. Asante said physicians and public health agencies should do more to educate women about the
dangers of drinking during pregnancy. He also recommended that doctors who suspect a patient may
be suffering from FASD contact agencies like his or other multidisciplinary programs across the
country that specialize in FASD diagnosis and treatment.

[Sidebar]
Dr. Kwadwo Asante criticized a recent study that claimed drinking small amounts of alcohol during
pregnancy was safe, as it relied on patient reports of use and did not track children for enough time.

To read about the Dr. Yvonne Kelly study, please refer to NOFAS-UK Fetal Alcohol Forum Issue 4 -
Low level studies from Australia and the UK and critical reviews

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Reflecting the recent increased public awareness of the topic, this is the first and most comprehensive resource for over a decade on the molecular basis, prevalence, treatment options, socioeconomic impact and prevention strategies of FASD.

Edited by world-renowned experts, this compendium includes the latest research results to provide new insights and realistic estimations of FASD frequencies in Western communities.

An invaluable resource for every professional dealing with the diagnosis, prevention and treatment of FASD, from researchers via health professionals to social workers.


Rod Densmore offers a unique perspective on FASD-related issues as both a medical practitioner and a parent of a young adult with FASD. With the intention of adding a practical, well-referenced, accessible, engaging and inexpensive teaching tool to existing resources, Densmore has successfully compiled research findings on a large variety of topics relevant to FASD and translated them into user-friendly language. He addresses the complexity of these issues through the expertise of a medical professional, yet with the sensitivity and passion that comes from parenting a person with FASD.

FASD Relationships includes a book and five DVD set, with each chapter of the book forming a series of modules about FASD. While the chapters build on each other, most can be used as stand-alone topics addressing common strengths and challenges for individuals exposed to alcohol prenatally. Densmore looks at both prevention and intervention concepts from a positive and proactive position, addressing commonly discussed concerns and areas of new research, including emerging fields such as epigenetics and neuroplasticity. The text offers practical considerations for approaching concerns like crisis management, suicide, trauma, and emotional regulation in the contexts of primary characteristics and secondary disabilities.

Through a combination of text, video and narrated PowerPoint slides, FASD Relationships examines topics such as the basics of FASD, genetics and FASD, sensory processing, neurobiology of FASD, neurobiology of attachment, brain development, music therapy, the value of relationships through
attachment and social connection neuroscience, epidemiology of FASD, and FASD resources. Densmore incorporates a variety of voices of FASD stakeholders, including an interview with Myles Himmelreich, an adult with FASD, and narratives from family members, caregiving professionals and service providers. Densmore incorporates information from many previously existing resources, examining and building upon them in the context of FASD. Topics covered are largely intended for a general audience, with certain sections designed for health professionals and those with keen interest in those specific perspectives.

FASD Relationships is available for purchase through Minga Marketplace on the Asante Centre website...."

www.asantecentre.org
Click on Minga Marketplace

❖ ALCOHOL, DRUGS AND MEDICATION IN PREGNANCY
The Long Term Outcome for the Child
Clinics in Developmental Medicine
Preece, Philip M. / Riley, Edward P. (eds.)
83.90 Euro
2011. 256 Pages, Hardcover

This book documents the consequences of the exposure of infants to the influence of intrauterine chemicals. In setting out the evidence for these outcomes, the authors demonstrate that decisions about care and management can and should be made as early as possible. This should allow professionals to provide protective management and prevent the delays that are so often seen in this area of medical and social care.

The international team of contributors sets out to inform the reader of the potential risks to infants exposed to a range of intrauterine chemicals that are potentially neuroactive, including medicinal drugs such as antiepileptics, antidepressants and antipsychotics, as well as drugs of abuse, including alcohol, opiates, and recreational drugs such as cannabis and tobacco. They review the teratogenic action of some of the chemical processes and the relationship of exposure to the stage of pregnancy. Some agents alter anatomic structure; others alter the chemical balance of neurotransmitters and may thus alter the regulation of brain function, with profound effects on the child's behaviour and propensity to behavioural disturbances. The book explores strategies to support these children and those who care for them, including statutory agencies.

Readership
Paediatricians, neonatologists, obstetricians, gynaecologists, child and adolescent psychiatrists and psychologists, those working in child care and child protection.

http://www.wiley-vch.de/publish/en/books/newTitles201101/1-898683-88-3/?sID=edjvv58v87d2bqfkbb2un5q98o2

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Teratogenic effects of Ethanol Vapour exposure on chick embryos
Kiran Kamran,1 Muhammad Yunus Khan,2 Liaqatali Minhas3
Department of Anatomy, Foundation University Medical College,1 Regional Center, College of Physician & Surgeons,2
Yusra Medical & Dental College,3 Islamabad.

Abstract

Objective: To observe the effect of ethanol vapours on chick embryos regarding developmental defects and hatchability characteristics.

Methods: An experimental study was performed in the Department of Anatomy at the Regional Center of College of Physicians and Surgeons, Islamabad, from February, 2006 to February, 2007.

Chicken eggs after having been exposed to ethanol vapours produced in a specially designed glass chamber, were dissected on day 7, day 10 and day 22 or on hatching and compared with age-matched controls. A breathalyzer was used for monitoring level of ethanol vapours inside the incubator.

Results: The results show that experimental group had comparatively more cases of delayed and assisted hatchings as well as growth retardation resulting into failure of retraction of yolk sac, as compared to the controls.

Conclusion: Ethanol vapour exposure increases the risks of developmental defects with increasing embryonic age. Increased duration of exposure, causes delayed hatching and more assisted hatchings. Newly hatched alcohol exposed chicks showed diminished locomotor activity and poor balance.

Keywords: Chick embryo, Ethanol vapours, Growth retardation (JPMA 61:328; 2011).

Materials and Methods

The study design of this project was experimental. Chick embryos were exposed to ethanol vapours and compared with controls. The project was carried out at Department of Anatomy, Regional Centre, College of Physician and Surgeon, Islamabad between February 2006 to February 2007.

A total of 180 'Desi' ('Desi' is a term used in the South Asian region to refer to poultry animals which are strictly fed an organic vegetarian-alone diet, without any animal or unnatural sources fed to them, thus precluding any artificial effects on the animals from artificial, blended or non-organic feeds) chicken eggs collected from Poultry Research Institute, Punjab, and Rawalpindi were divided into control group A and experimental group B of 90 eggs each. The day when eggs were placed in the incubator was taken as day 1. Each group was further subdivided into 3 subgroups based on the day of sacrifice or hatching. Subgroup 1 was sacrificed at
day 7. Subgroup 2 was sacrificed at day 10. Subgroup 3 was dissected at day 22 or on hatching whichever was earlier. Eggs which were cracked or stored in the refrigerator were excluded from the study.

Group B1 was exposed to ethanol vapours from day 1 to 6. The embryos in this group were scheduled to be sacrificed on day 7. The embryos to be sacrificed on day 10 were exposed to ethanol vapours from day 1 to 9. The chicks that were dissected either at day 22 or else on hatching, whichever was earlier, were exposed to ethanol vapours from day 1 to 9.

An incubator with capabilities of maintaining and monitoring temperature, humidity and for turning the eggs periodically was used for incubating the eggs. The temperature in the incubator was maintained at 102°F and the relative humidity was kept between 70% to 80%.

Ethanol vapours were produced in the glass chamber containing ethanol into which air was bubbled with the help of an air pump. The glass chamber was completely sealed to prevent the leakage of vapours from the chamber. The flow of air into the glass chamber was adjusted with the help of a valve which was built within the plastic tube leading from the air pump. Vapours collected in the chamber were transmitted into the incubator through a plastic pipe fitted with an adjustable clamp for controlling vapour flow. Concentration of ethanol in the incubator was maintained in the range of 0.75mg/l to1.5mg/l. This dose was determined with the help of a preliminary project.

Ethanol vapour level in the incubator was checked and maintained by using a breathalyzer (CA 2000 of Viper technologies USA). Breathalyzer gives the blood alcohol concentration (BAC). The leaflet for the device tells that 0.01% BAC is equal to 0.05mg/l of BRAC (Breath alcohol concentration). This information was used for conversion of BAC to BRAC.

The day 7 and day 10 embryos were dissected out by cutting chorioallantoic membrane and amnion.

Some chicks hatched by day 22 while other chicks which could not hatch by themselves till day 22 were manually taken out by breaking the shells.

The day and mode of hatching of chicks was noted. Mode was either normal or assisted. The chick embryos and newly hatched chicks were examined for any gross abnormalities, abnormal gait, posture and any other abnormal behaviour as compared to the control.

Chi-square test was used for analyzing the day and mode of hatching. Percentages of newly hatched chicks with gross abnormalities in both control and alcohol exposed group were used for calculating p value by applying student t test for percentages.

Results

1. Day of Hatching: In the present study control group A3 had significantly more hatchings on day 21 as compared to experimental group B3 which had more hatchings on day 22 (Table). In other words, experimental group B3 had more delayed hatchings as compared to the control group A3.

2. Mode of Hatching: The mode of hatching was either normal or assisted. In normal hatching, the chick hatched by itself. In assisted hatching, the shells were manually broken and chicks were drawn out. In assisted hatchings some chick embryos were able to start the process of piping by cracking their shells but were unable to hatch out of their shells. In experimental group, assisted hatchings were more than normal

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Day 21 Normal</th>
<th>Day 21 Assisted</th>
<th>Day 22 Normal</th>
<th>Day 22 Assisted</th>
<th>Total</th>
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<tr>
<td>A3</td>
<td>23</td>
<td>0</td>
<td>23</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>B3</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td>16</td>
<td>20</td>
</tr>
</tbody>
</table>

A3=Newly hatched control chicks.
B3=Newly hatched alcohol exposed chicks.
p-value of difference between A3 & B3 regarding the day of hatching=0.001.
p-value of difference between A3 & B3 regarding the mode of hatching=0.000.
hatchings as compared to control group which had less assisted hatchings (Table). The difference between the two hatchings was found to be statistically significant (p = 0.000).

3. Gross Examination of Chicks and Embryos: The newly hatched chicks of the group B3 showed behavioral changes. A total of 33% chicks demonstrated wobbly gait, staggering, and poor balance. Whereas 56% of chicks showed diminished mobility and were unable to stand erect (Figure-1). In all 90% of newly hatched chicks of control group were active and healthy while 10% were taken out through assisted hatching and showed diminished mobility.

On gross examination of subgroup 3, it was seen that there was failure of retraction of yolk sac into the abdominal cavity in the experimental chicks (Figure-2). Yolk sac starts retracting back into the abdominal cavity at day 19 and this retraction is completed at day 20.8 There was only 1 chick in subgroup A3 (out of 30) and 9 chicks in subgroup B3 (out of 30) which had failure of retraction of yolk sac. Failure of retraction of yolk sac was significantly more in experimental group B3 than that of control group A3 (p=0.000). No gross abnormalities were seen in day 10 and day 7 embryos in both dead and living chick embryos in the experimental group.

**Discussion**

1) Day and Mode of Hatching: The control group A3 had significantly more hatchings on day 21 as compared to experimental group B3 which had more hatching on day 22. In other words, experimental group B3 had more delayed hatchings as compared to the control group A3. The mode of hatching was either normal or assisted. In normal hatching, the chick hatched by itself. In assisted hatching, the chicks either failed to pip the eggshell or failed to come out after piping the shells, again leading to a delay in hatching. In experimental group, assisted hatchings were more than normal hatchings as compared to control group which had less assisted hatchings. The comparison between the two hatchings was found to be highly significant (p = 0.000). The cause of delayed hatching was either dead chicks or chicks who had diminished mobility. The hypoactivity could probably have been due to the central nervous system damage after ethanol exposure for the initial 9 days of incubation. Prenatal alcohol exposure showed several structural abnormalities including reduction of brain size, prominent brain shape abnormalities with narrowing in the parietal region and reduced brain growth in portions of the frontal lobe seen through certain neuroimaging techniques. Certain areas of brain are more prone to prenatal alcohol exposure, as seen in volumetric and tissue density studies. These studies showed disproportionate reductions in the parietal lobe, cerebellar vermis and the caudate nucleus.8

Foetal alcohol syndrome is accompanied with muscle weakness, muscle wasting, and atrophy which could be another cause of hypoactivity in these chicks. David and Subramaniam9 assessed the effects of prenatal alcohol exposure on the developing rat neuromuscular system by injecting pregnant Sprague-Dawley rats intraperitoneally with 1.0 ml of 20% ethyl alcohol. Unexposed rats served as controls. There was a high proportion of polynoeuronally innervated endplates at the neuromuscular junction in the alcohol-exposed rats. The muscle weights, as well as the number and size of the muscle fibers, were significantly reduced in these animals showing muscle atrophy. A light-microscopic examination of the nerve sections revealed alterations in the connectivity of myelin. The finding that a higher proportion of endplates were polynoeuronally innervated in the alcohol-exposed rats indicates that the maturation process of the neuromuscular system was delayed, thus confirming the deleterious effects of alcohol on growth and maturation of the nerve-muscle system leading to hypoactivity.9 Myocyte atrophy and death are the main pathological findings. Pathogenic mechanisms are pleiotropic, the most relevant being disturbances in carbohydrate, protein, and energy cell turnover, signal transduction, and induction of apoptosis and gene dysregulation.10

Alcohol causes skeletal muscle atrophy and death by damaging its metabolism. Insulin plays an important regulatory role in glucose uptake and utilization in skeletal muscle. Alcohol can acutely reduce the normal metabolic responses of skeletal muscle to the action of insulin which causes acute impairment in glucose metabolism. Skeletal myopathies due to alcohol are believed to result from abnormalities in synthesis of muscle protein.11

2) Gross Examination of Chicks and Embryos: The newly hatched chicks of the experimental group showed behavioural changes. Thirty three percent chicks demonstrated wobbly gait, staggering, and poor balance.
Nancy Morris and colleagues\textsuperscript{12} used a chick model in which adults chicks of 2 months age were given ethanol by diluting it in their drinking water. The birds demonstrated wobbly gait, staggering, and poor balance. The most important organ in this regard is cerebellum which is basically responsible for equilibrium and balance. Researchers have utilized quantitative structural magnetic resonance imaging (MRI) to examine the brains of living children and adults with histories of heavy prenatal alcohol exposure. These studies indicated structural abnormalities in various regions of the brain, including the cerebellum.\textsuperscript{13}

In this study 56\% chicks showed diminished mobility and were unable to stand erect. Another probable cause of hypoactivity could be alcohol withdrawal. Slawecki and Roth\textsuperscript{14} exposed male Sprague Dawley rats to ethanol vapour for 12 or 14 days and then assessed their locomotor activity. Hypoactivity emerged rapidly in rats during ethanol withdrawal. Withdrawal induced hypoactivity was also seen in studies conducted on different species of rats after ethanol intake by other routes.\textsuperscript{15,16}

In the present study experimental group B3 showed a predominant failure of retraction of yolk sac into the abdominal cavity. Normally, yolk sac starts retracting back into the abdominal cavity at 19th day and this retraction is completed at day 20.\textsuperscript{17} Failure of retraction of yolk sac was significantly more in experimental group B3 than that of control group A3, which is a sign of growth retardation leading to this ventral body wall defect. In a study by Joydeep,\textsuperscript{18} chick embryos were exposed to single doses of 5\%, 10\% and 15\% ethanol, and the effects on general growth and development of these chicks were studied. There was significant growth retardation found in these chicks which is in accordance with this study. In another study chick embryos were explanted in shellless cultures and single dose of 50\% ethanol was applied. Ethanol significantly increased the mortality rate and induced growth retardation.\textsuperscript{19} Experimental studies on other species show that apoptosis, oxidative stress, altered cell cycle, suppressed DNA and protein synthesis are some of important causes of ethanol induced deformities.\textsuperscript{20,21} No gross abnormalities were seen in day 10 and day 7 embryos in both dead and living chick embryos in the experimental group which shows that both increase duration of exposure and increasing embryonic age enhances the risk of growth retardation and developmental defects in developing chick embryos.

**Conclusion**

Ethanol vapour exposure increases the risks of developmental defects with increasing embryonic age and increased duration of exposure. Hatching is delayed and there are more assisted hatchings. Newly hatched alcohol exposed chicks showed diminished locomotor activity and poor balance which may be attributed to damage to central nervous system or skeletal muscle.

**References**

A *Drosophila* model for fetal alcohol syndrome disorders: role for the insulin pathway

Kimberly D. McClure1,*, Rachael L. French1,*,‡ and Ulrike Heberlein1,2,§

**SUMMARY**

Prenatal exposure to ethanol in humans results in a wide range of developmental abnormalities, including growth deficiency, developmental delay, reduced brain size, permanent neurobehavioral abnormalities and fetal death. Here we describe the use of *Drosophila melanogaster* as a model for exploring the effects of ethanol exposure on development and behavior. We show that developmental ethanol exposure causes reduced viability, developmental delay and reduced adult body size. We find that flies reared on ethanol-containing food have smaller brains and imaginal discs, which is due to reduced cell division rather than increased apoptosis. Additionally, we show that, as in mammals, flies reared on ethanol have altered responses to ethanol vapor exposure as adults, including increased locomotor activation, resistance to the sedating effects of the drug and reduced tolerance development upon repeated ethanol exposure. We have found that the developmental and behavioral defects are largely due to the effects of ethanol on insulin signaling; specifically, a reduction in *Drosophila* insulin-like peptide (Dilp) and insulin receptor expression. Transgenic expression of Dilp proteins in the larval brain suppressed both the developmental and behavioral abnormalities displayed by ethanol-reared adult flies. Our results thus establish *Drosophila* as a useful model system to uncover the complex etiology of fetal alcohol syndrome.

**INTRODUCTION**

The ability of alcohol to cause developmental anomalies has been demonstrated in a broad range of taxa, from insects to mammals. In humans, alcohol consumption during pregnancy can result in fetal alcohol syndrome (FAS), which consists of a persistent growth deficiency, craniofacial dysmorphology and deficient brain growth associated with associated neurocognitive deficits (Jones and Smith, 1973). FAS is the leading known cause of congenital mental retardation in the Western world (Pulsifer, 1996), and the most severe form of a broad range of disorders known as fetal alcohol spectrum disorder (FASD) (Hoyme et al., 2005). The prevalence of FAS in the world is one to three per 1000 births, indicating a serious medical and societal problem (May and Gossage, 2001). Despite the growing awareness of FAS and FASD (FAS/FASD) and posted warnings on alcoholic beverages, consumption of alcohol during pregnancy continues, highlighting the need for an understanding of the molecular basis of FAS and developing novel treatments to mitigate the complications of gestational ethanol exposure.

The long-lasting neurobehavioral impairments are arguably the most serious consequences of FAS/FASD. Individuals with FAS can exhibit deficits in attention, memory and motor coordination, display hyperactivity, and can suffer from disturbances in food consumption and sleep (Clarren and Smith, 1978; Eckardt et al., 1998). Animal models have shown that adult responses to ethanol are significantly altered by developmental ethanol exposure. For instance, adult mice exposed prenatally to ethanol have been reported to be more sensitive to the locomotor stimulating effects of low doses of ethanol (Becker et al., 1993), be resistant to the disruptive effects of ethanol on operant responding (Middaugh and Ayers, 1988), and be defective in the development of tolerance to the motor incoordinating effects of ethanol (Becker et al., 1996). These behavioral changes are directly linked to the sensitivity of the developing nervous system to the toxic effects of ethanol. Numerous studies have shown that damage to the nervous system is related to the timing, pattern and dose of alcohol exposure during fetal development. For example, a single ethanol exposure in mice administered 7 days after birth (P7; equivalent to the third trimester of pregnancy in humans) causes generalized loss in brain mass (Samson and Diaz, 1981), whereas earlier exposure leads to less deleterious effects (Tran et al., 2000). Conversely, studies in primates have found that earlier exposures to ethanol are as damaging as longer exposures that also included the earlier time window (Clarren et al., 1992; Schneider et al., 2001). This was also observed in zebrafish, in which early ethanol exposure, from midblastula to organogenesis, causes most of the ethanol-induced developmental defects (Reimers et al., 2004). Intriguingly, most of the ethanol sensitivity periods correlate with episodes of intense cellular growth and proliferation (Ikonomidou et al., 2000). Whether these periods of sensitivity are also relevant to the behavioral alterations associated with FAS/FASD has not been examined.

The timing of critical periods of alcohol sensitivity and the mechanisms by which ethanol exposure during these periods affects both development and adult behavior can be investigated using *Drosophila melanogaster*, the common fruit fly. The use of *Drosophila* for the study of FAS/FASD-like disorders is sensible for a number of reasons: first, previous studies have shown that flies are susceptible to the developmental toxicity of ethanol; larvae reared on ethanol-containing food exhibit appendage abnormalities (Ranganathan et al., 1987a; Ranganathan et al., 1987b). Second, the external development of flies eliminates the complications of
maternal-placenta-fetal interactions seen in mammalian studies. Adult females lay embryos (eggs) that hatch as larvae after 1 day. These larvae grow tremendously over the next 4 days as they voluntarily consume food, and molt twice. During the final larval instar, larvae stop eating, leave the food (wander) and form a puparium, signaling the onset of metamorphosis. The duration of metamorphosis is 4 days, after which the adult fly emerges. Thus, the life cycle of the fly is such that developmental ethanol exposure and the consumption of ethanol-containing food are voluntary, unlike gestational mammals, and occurs mostly during the larval stage of development; involuntary ethanol exposure during metamorphosis can, however, be achieved experimentally. Third, flies allow for mutagenesis screens, which, coupled with gene cloning and genetic pathway analysis, can be used to identify and elucidate mechanisms underlying ethanol teratogenesis. This is important given that genetic factors have been shown to modulate numerous aspects of alcohol-related disorders, including those of FAS (Ducci and Goldman, 2008).

The molecular mechanisms underlying FAS/FASD are complicated owing to the fact that ethanol and its metabolic products interact with many different gene products in a diversity of developing tissues. Studies have attributed the teratogenic effects of alcohol to ethanol metabolism and related oxidative stress (Kotch and Sulik, 1992), to neuronal cell loss and migration defects (Ikonomidou et al., 2000; Rovasio and Battiato, 1995), to changes in DNA methylation patterns (Kaminen-Ahola et al., 2010; Liu et al., 2009), and to a reduction in retinoic acid production (Yelin et al., 2005). Previous work has also shown that developmental ethanol exposure inhibits both trophic and neurotrophic growth factors and/or their signal transduction pathways. For example, developmental ethanol exposure inhibits the expression of insulin, insulin-like growth factor (IGF)-II, and the IGF-I and -II receptors in the rodent brain (de la Monte et al., 2005). In addition, IGF-I is protective against ethanol-related neuronal toxicity in cultured neurons (Barclay et al., 2005) and ameliorates the motor coordination defects caused by developmental alcohol exposure in rats (McGough et al., 2009). The ability of ethanol to interfere with growth factor signaling, and insulin and/or IGF signaling in particular, has numerous effects, including those on cell proliferation, growth, viability, energy metabolism and synapse formation (Luo and Miller, 1998).

In Drosophila, as in mammals, organismal and cellular growth is regulated by the insulin signaling pathway. There are seven Drosophila insulin-like peptides (Dilps), which govern growth, fat and carbohydrate metabolism, reproduction, and longevity (Geminard et al., 2009). The Dilp genes are expressed in a variety of larval and adult tissues, and their products activate a common insulin receptor (InR) (Brogiolo et al., 2001; Chen et al., 1996). Four Dilps, encoded by the dilp1, dilp2, dilp3 and dilp5 genes, are expressed in a small subset of specialized neurosecretory cells, the insulin producing cells (IPCs). These Dilps show overlapping expression patterns and are necessary to drive the extensive growth occurring during larval development (Gronke et al., 2010). Ablation of the IPCs during larval development leads to reduced body size, developmental delay and lethality, phenotypes that are similar to what is observed with mutants in the InR (Broughton et al., 2005; Chen et al., 1996; Ikeya et al., 2002; Rulifson et al., 2002). The expression of dilp6 in the fat body controls growth, specifically during pupal development (Okamoto et al., 2009; Slaidina et al., 2009), whereas dilp4 and dilp7 are not involved in growth regulation, but instead have possible roles in axon guidance and female fecundity, respectively (Gronke et al., 2010; Yang et al., 2008; Song et al., 2003).

Here we present a Drosophila model of alcohol-induced teratogenesis that exhibits several features of FAS, including profound changes in adult behavior. We find that flies reared continuously on ethanol-containing food show a dose-dependent developmental delay, reduced eclosion as adults, a reduction in adult mass and altered behavioral responses to vaporized ethanol as adults. We demonstrate that many of these phenotypes can be attributed to ethanol interfering with the insulin signaling pathway in the brain, specifically with the expression of dilp2 and InR. We demonstrate that Dilp expression in the brain and in the whole larva can ameliorate both the developmental and behavioral alterations associated with developmental ethanol exposure. Our findings validate Drosophila as a useful animal model to uncover the molecular basis of FAS. Thus, studies of ethanol teratogenesis in Drosophila should provide new and complimentary mechanistic insights into the toxicity of developmental ethanol exposure in mammals, including humans.

![Fig. 1. Ethanol-reared flies show reduced viability and developmental delay.](image)

(A) The percentage of flies undergoing eclosion (mean ± s.e.m.) differs between control (0% ethanol) and ethanol-reared flies (5, 10 and 12% ethanol-food) (Dunnett’s, n=10, *P<0.0001). (B) Duration of development (from egg to adult) is prolonged by ethanol-rearing conditions. Cumulative eclosion rates (percentage of flies undergoing eclosion) of ethanol-reared flies differ from that of control flies (repeated measures ANOVA, n=10, *P<0.0001 between and within groups). Time to 50% total eclosion (at which 50% of flies had eclosed) differs between ethanol-reared and control flies and is indicated with arrowheads (Dunnett’s, n=10, *P<0.0001). Colors correspond to treatment groups shown in A. (C) At eclosion, adult mass is reduced by developmental ethanol exposure (Kruskal-Wallis tests, n=6, *P=0.0032 and 0.0242 for adult females and males, respectively).
RESULTS
Ethanol-reared flies display reduced viability and have developmental delay
To establish *Drosophila* as a model system to investigate FASD, we first determined the optimal ethanol-dosing regimen to induce developmental toxicity in flies. From embryogenesis until adult eclosion, flies of our wild-type strain, white1118 Berlin (wB), were reared on media supplemented with 0, 5, 10 or 12% ethanol. To avoid evaporation of the ethanol in the food and to expose flies during metamorphosis (when they do not feed), the vials in which the flies develop were placed in a water bath (controls) or in a 5% ethanol bath (experimental), and the duration of development and adult eclosion rates were monitored (see Methods for a more detailed protocol). There was a striking decrease in the number of flies undergoing adult eclosion in groups reared on ethanol food compared with control groups, with the effect being more severe at higher ethanol concentrations (Fig. 1A). This reduced eclosion was due to lethality during both the larval and pupal stages; only a fraction of larvae developed to the pupal stage and, of the pupae that formed, only a fraction eclosed as adult flies (supplementary material Fig. S1A).

In addition to decreasing viability, ethanol exposure during development significantly slowed the rate of egg-to-adult development (Fig. 1B). On regular media, wB flies began eclosion 10 days after egg laying (AEL), with 50% total eclosion (the point at which 50% of the flies have eclosed) occurring by 10.2 AEL (Fig. 1B). By contrast, wB reared on 5%-ethanol food began eclosion with a 1-day delay, 11 days AEL, and 50% total eclosion occurred 11.3 days AEL (Fig. 1B). Flies reared on 10- and 12%-ethanol food were more severely delayed to eclosion, as 50% total eclosion was observed 13.1 and 14.3 days AEL, respectively (Fig. 1B). A detailed analysis of the developmental delay revealed that the duration of only the second and third larval instars was affected by ethanol exposure (supplementary material Fig. S1B), whereas the duration of metamorphosis was normal (data not shown). In contrast to a previous study, our ethanol-rearing protocol did not cause adult patterning defects (at any concentration tested) (Ranganathan et al., 1987a); however, at the time of eclosion, both female and male flies had decreased body weight (Fig. 1C). Importantly, we found that the presence of ethanol (5%) in the food did not significantly alter larval food consumption (supplementary material Fig. S2); the developmental delay, lethality and reduced body size are therefore not due to lack of nutrition. Finally, adult lifespan was not affected by developmental ethanol exposure (5%; supplementary material Fig. S1C). These data indicate that developmental ethanol exposure is detrimental to the correct timing of development and to survival to adulthood.

Ethanol-reared flies exhibit neurobehavioral changes
Because fetal ethanol exposure in mammals leads to altered adult responses to ethanol exposure (Middaugh et al., 1988; Becker et al., 1993) (for a review, see Becker et al., 1996), we tested adult flies reared in 5% ethanol for their responses to the stimulating and sedating effects of ethanol vapor as well as their ability to develop tolerance to ethanol-induced sedation.

We exposed adult flies reared on 5% ethanol to a concentration of ethanol vapor that stimulates locomotor activity and analyzed their behavior using a locomotor tracking assay (Wolf et al., 2002) (Fig. 2A). In control flies, which were not exposed to ethanol during development, this concentration of ethanol vapor caused a transient olfactory startle response (first minute) that was followed by a sustained period of enhanced locomotor activity. As the concentration of internal ethanol increased, flies slowed down and began to sedate. This pattern is very similar to that seen in mice, where low doses of ethanol stimulate locomotion, whereas higher doses lead to motor incoordination and, eventually, sedation (Phillips and Shen, 1996). Flies reared in 5% ethanol displayed significantly increased and sustained locomotor activation when exposed to ethanol vapor as adults, achieving, on average, a velocity 1.6 mm/second faster than that seen in control flies (grown on food without ethanol). Thus, ethanol exposure during development leads to increased sensitivity to the locomotor activating effects of ethanol in adulthood.

Next, we tested whether ethanol-reared adult flies displayed altered responses to ethanol-induced sedation. We exposed flies to a sedating concentration of ethanol vapor and examined the flies for loss of the righting reflex (LORR) at defined intervals throughout the exposure. We found that the time needed for 50% of control

![Fig. 2. Flies reared in ethanol display permanent neurobehavioral changes. (A) Ethanol-reared flies display increased locomotor hyperactivation when exposed to a moderate concentration of ethanol vapor. Flies were exposed to a 70:80 ratio of vaporized ethanol:humidified air (E/A) starting at time 0. Ethanol-reared flies achieved a peak velocity of 8.2 mm/second, compared with 5.6 mm/second for control flies (Student's t-test, n=8, *P<0.001). (B) Ethanol-reared flies are resistant to ethanol-induced sedation. Upon exposure to a high (100:50 E/A) concentration of ethanol, control flies achieved 50% sedation 4.6 minutes sooner than ethanol-reared flies, reflecting a 34% increase in sedation resistance for flies reared on ethanol (Student's t-test, n=12, *P<0.001). (C,D) Ethanol-reared flies are defective in tolerance development. Flies were exposed to a sedating dose of ethanol (110:40 E/A), allowed to rest for 4 hours and then exposed to a second dose; sedation times were calculated for each exposure. Control flies require an additional 9 minutes to achieve ST50 upon a second exposure, indicating the development of functional ethanol tolerance. Ethanol-reared flies develop only 4.1 minutes of tolerance (Student's t-test, n=12, *P<0.019). In all experiments, flies were transferred as first-instar larvae to media containing 5% ethanol, collected upon eclosion, and behavioral tests were performed 2 days later.](image-url)
flies to become sedated (ST50) was 13.6 minutes, whereas flies reared on food containing 5% ethanol had an ST50 of 18.2 minutes (Fig. 2B). Thus, flies reared on 5% ethanol showed a 34% increase in ST50, a marked resistance to the sedating effects of ethanol.

Finally, we tested flies reared on 5% ethanol for their ability to develop tolerance to the sedating and/or motor incoordinating effects of ethanol exposure (Fig. 2C,D). We exposed adult flies to a sedating concentration of ethanol vapor for 35 minutes, calculated the ST50 for the first exposure, then, 4 hours later, exposed them to a second dose of ethanol vapor. Control flies (reared in the absence of ethanol) showed ST50 of 10.4 and 19.1 minutes during the first and second exposures, respectively. The difference in ST50 between the second and first ethanol vapor exposures, 8.7 minutes, is defined as tolerance (Berger et al., 2008). Ethanol-reared flies, as expected, had a higher ST50 (15.7 minutes) during their first ethanol vapor exposure, which increased to 19.8 minutes during the second exposure. Thus, ethanol-reared flies showed an increase of ST50 of only 4.1 minutes, a reduction of approximately 47% relative to control flies. It is possible that the tolerance defect we observed in the ethanol-reared adult flies might be due to a ceiling effect of the assay during the second ethanol exposure. However, we believe that this is not the case because we have found that many ethanol-resistant mutants can develop normal ethanol tolerance (Berger et al., 2008). Furthermore, it is possible to generate ethanol-reared flies with normal sedation sensitivity that nevertheless are defective in the development of ethanol tolerance (see later). Taken together, these results suggest that regions of the nervous system and/or specific signaling mechanisms that are required for establishing normal ethanol sensitivity and tolerance in the adult fly are altered by exposure to ethanol during development.

Ethanol-reared adult flies showed normal ethanol absorption and metabolism (supplementary material Fig. S3). In addition, western blot analysis showed that expression of alcohol dehydrogenase, the principal metabolizing enzyme for ethanol, was not different between adult ethanol-reared and control flies (data not shown). It should be noted that adult flies exposed to ethanol during development have long metabolized the ethanol when tested for adult ethanol behaviors (supplementary material Figs S3 and S4). These data indicate that the ethanol sensitivity phenotype of ethanol-reared flies is not caused by altered drug pharmacokinetics.

**Critical periods of ethanol toxicity**

Studies in mammals, including humans, have shown that both the timing and duration of ethanol exposure are important factors in the development of FAS (Sulik et al., 1981; Sulik et al., 1986). To assess the critical periods during which developmental ethanol exposure leads to a decline in adult viability and developmental delay, we reared wB flies on 5%-ethanol food during discrete developmental stages. For example, ethanol exposure was limited to embryogenesis, larval or pupal stages, or, alternatively, to a combination of these developmental stages (Table 1).

Exposure to 5% ethanol during embryogenesis did not affect adult viability or time to eclosion, most probably because ethanol does not cross the eggshell. Ethanol exposure that was limited to larval development, by contrast, caused a 1-day delay in eclosion and a reduction in adult viability from 93% in control flies to 63% in ethanol-reared flies. When ethanol exposure was restricted to the pupal stage, there was a small but significant decline in adult viability, yet developmental timing was normal (Table 1). These results confirm that the developmental delay induced by ethanol is solely due to exposure during the larval stages, whereas the reduced viability has both larval and pupal components. The effects of ethanol were also examined during individual larval stages and, interestingly, exposure to ethanol during either the second or third larval instars resulted in a developmental delay, whereas a decline in adult viability was only observed with exposure during the third larval instar (Table 1). Thus, both the second and third larval instars are particularly sensitive to the toxic effects of developmental ethanol exposure. Taken together, these data demonstrate that the critical time period for ethanol toxicity in flies is primarily during larval development, although ethanol exposure during metamorphosis also contributes to the decline in adult viability.

Next, we determined whether the neurobehavioral phenotypes were due to ethanol exposure during distinct developmental time periods (Table 2). Flies were transferred from regular to ethanol-containing food (5%) at specific larval stages and allowed to complete development before being tested for acute ethanol sensitivity and tolerance as adults. As expected, flies grown on ethanol-containing food throughout development displayed increased sedation resistance and reduced tolerance development.

### Table 1. Critical periods of ethanol toxicity: survival and developmental delay

<table>
<thead>
<tr>
<th>Ethanol exposure</th>
<th>% survival to adult (± s.e.m.)</th>
<th>Delay (&gt;24 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No exposure</td>
<td>93±1.87</td>
<td>No</td>
</tr>
<tr>
<td>E, L, M</td>
<td>54±2.70*</td>
<td>Yes</td>
</tr>
<tr>
<td>E</td>
<td>90±3.04</td>
<td>No</td>
</tr>
<tr>
<td>L</td>
<td>63±2.12*</td>
<td>Yes</td>
</tr>
<tr>
<td>M</td>
<td>76±4.72*</td>
<td>No</td>
</tr>
<tr>
<td>E, L</td>
<td>63±4.04*</td>
<td>Yes</td>
</tr>
<tr>
<td>E, M</td>
<td>80±3.55*</td>
<td>No</td>
</tr>
<tr>
<td>L, M</td>
<td>48±2.47*</td>
<td>Yes</td>
</tr>
<tr>
<td>L1</td>
<td>92±2.33</td>
<td>No</td>
</tr>
<tr>
<td>L2</td>
<td>90±2.6</td>
<td>Yes</td>
</tr>
<tr>
<td>L3</td>
<td>56±3.4*</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Data shown are comparisons of survival and developmental delay between 0% and 5% ethanol exposure at discrete developmental stages and combinations of developmental stages. E, embryogenesis; L, larval development; M, metamorphosis; L1, first larval instar; L2, second larval instar; L3, third larval instar. *P<0.006, Dunnet’s, n=6 vials containing 100 animals each.

### Table 2. Critical periods of ethanol toxicity: behavior

<table>
<thead>
<tr>
<th>Ethanol exposure</th>
<th>ST50 (minutes)</th>
<th>Tolerance (% of control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No exposure</td>
<td>15.9±1.0</td>
<td>100±6.5</td>
</tr>
<tr>
<td>E, L, M</td>
<td>23.0±1.8*</td>
<td>69±7.4*</td>
</tr>
<tr>
<td>L, M</td>
<td>23.2±2.0*</td>
<td>68±6.2*</td>
</tr>
<tr>
<td>L2, L3, M</td>
<td>22.9±2.1*</td>
<td>71±11.7</td>
</tr>
<tr>
<td>L3, M</td>
<td>16.5±2.1</td>
<td>69±5.2</td>
</tr>
</tbody>
</table>

E, embryogenesis; L, larval development; M, metamorphosis; L2, second larval instar; L3, third larval instar. Each rearing condition represents six vials of 100 animals/vial (n=6). Data are presented as mean ± s.e.m. *P<0.05, one-way ANOVA with Tukey HSD post-hoc analysis.
compared with controls. Flies were similarly affected when transferred to ethanol-containing food as second-instar larvae, indicating that the critical period(s) for both phenotypes (adult resistance and tolerance) was during or after the second instar phase. When flies were transferred to ethanol-containing food as third-instar larvae, they showed sedation profiles indistinguishable from those of control flies (Table 2), indicating that the critical period for development of resistance to ethanol sedation is during the second larval instar. These flies, however, failed to develop normal ethanol tolerance (Table 2), indicating that the critical period for this phenotype is during or after the third larval instar phase. Importantly, we did not see a cumulative effect of longer exposure to ethanol: flies exposed to ethanol from the late-third-instar stage onwards showed the same reduction in tolerance as flies exposed to ethanol throughout development (Table 2). These data show that the critical periods of developmental ethanol exposure that lead to enhanced resistance to sedation (the second larval instar) and a reduced ability to develop tolerance (the third larval instar and pupal stage) are separable, suggesting that these two phenotypes are caused by distinct effects of ethanol on development.

To determine whether the differences we observed in ethanol toxicity, developmental delay and adult behavior had a pharmacokinetic basis, we measured the concentration of ethanol in animals exposed to developmental ethanol (5% ethanol). Ethanol-reared animals showed a steady increase of internal ethanol concentration during each larval instar, achieving a maximum internal ethanol concentration during metamorphosis (supplementary material Fig. S4). Such observations suggest that the discrete ethanol-sensitivity periods are not simply due to the rise of internal ethanol concentration during larval and metamorphic development, with each phenotype having a different ethanol concentration threshold, but rather that individual tissues and/or cells are differentially sensitive to ethanol at distinct developmental stages.

**Effects of developmental ethanol exposure on proliferation and apoptosis in the larval brain and the imaginal discs**

In a number of animal models, ethanol treatment causes increased apoptosis in the developing CNS, resulting in reduced brain mass (Ikonomidou et al., 2000; McGee and Riley, 2006). Ethanol exposure also alters the rate of neuronal cell division in the immature brain, reducing the number of new cells as well as deterring neural outgrowth (Guerri, 1998). We observed a reduction in larval brain size upon rearing flies on ethanol-containing food; compared with controls, brain lobes were reduced by 20% and 40% in larvae reared on 5%- and 10%-ethanol food, respectively (Fig. 3A-D). To determine whether the small CNS phenotype was due to increased apoptosis, we examined cell death in the brains of control and ethanol-reared larvae at various developmental stages (early-, mid- and late-third-instar larvae) by TUNEL labeling. The brains of control and ethanol-reared larvae showed nearly equivalent levels of cell death at each developmental stage examined (supplementary material Fig. S5; data not shown), indicating that the reduced size of the CNS was not due to ethanol-induced apoptosis.

To investigate defective proliferation as a possible mechanism for the small brain phenotype, we monitored replicating cells (S phase) by BrdU incorporation in the developing brains of both ethanol-reared and control larvae. Larvae were labeled with BrdU for 4 hours at the transition from the first to second larval instars and dissected for analysis as wandering late-third-instar larvae. All cells in the brain that undergo S phase during the labeling period incorporate BrdU, including neuroblasts, ganglion mother cells and immature neurons; their progenitors also retain BrdU label (Datta, 1995). Control larvae showed high levels of BrdU-labeled neurons in the larval brain lobes as well as in the ventral ganglion (Fig. 3A). By contrast, ethanol-reared larvae showed a drastic reduction of dividing cells in the larval CNS, both in the brain lobes and the ventral ganglion (Fig. 3B,C). In order to determine whether this pattern of defective proliferation also occurred during later larval stages, ethanol-reared and control larvae were labeled with BrdU at the transition from the second to third larval instar. Labeling at this later stage revealed an equivalent number of dividing cells in larvae reared on 0%- and 5%-ethanol food (supplementary material Fig. S6A,B). However, larvae reared on 10%-ethanol food showed a dramatic reduction in replicating cells in the brain (supplementary material Fig. S6C). These results are consistent with the small brain phenotype observed predominantly in larvae grown on 10%-ethanol food. Taken together, these data suggest that the small brain phenotype observed in flies reared on ethanol-containing food is caused by reduced proliferation, not enhanced apoptosis, and that distinct developmental periods are differentially sensitive to the effects of ethanol on proliferating CNS cells.

**Fig. 3. Developmental ethanol exposure causes defective proliferation in the larval CNS.** The number of replicating cells (S phase) in the CNS of control and ethanol-reared larvae was assessed by pulse labeling with BrdU at 24-28 hours post-hatching, with dissection of wandering third-instar larvae. Representative samples of brains from larvae reared on (A) 0% ethanol, (B) 5% ethanol and (C) 10% ethanol (40× magnification) are shown. Arrows indicate labeling in the mushroom body (MB), optic lobe (OL) and thoracic (T) neurons. (D) The size of brain lobes differs between ethanol-reared (5 and 10% ethanol) and control larvae (Dunnett’s, n=10, *P<0.0047).
We did not observe gross morphological defects in the adult CNS upon developmental ethanol exposure to 5%-ethanol food (data not shown); it is likely, however, that subtle defects were present but not easily detectable.

To investigate whether structures that are rapidly growing in larvae are generally affected by developmental exposure to 5% ethanol, we examined the growth of imaginal discs, the larval precursors of the adult fly appendages. As in the larval brain, imaginal discs of ethanol-reared larvae were significantly reduced in size compared with those of control larvae (supplementary material Fig. S7). To assess whether developmental ethanol exposure slowed cell proliferation in the imaginal discs, we used a heat-shock-induced flip-out GAL4 driver to induce permanent, heritable expression of GFP in random clones of cells (Neufeld et al., 1998). At 48 hours after heat shock, we counted the number of GFP-expressing cells per clone to determine in vivo rates of cell division. We found that cell-doubling time in the wing imaginal discs increased from 14.4±0.87 hours in control larvae to 18.5±0.61 hours in ethanol-reared larvae (Student’s t-test, P<0.0001; n=83 and 89 clones in control and 5%-ethanol-reared larvae, respectively). In addition, the small disc phenotype was not caused by abnormal morphogen signaling, because the expression of several morphogens in the wing imaginal discs of ethanol-reared larvae, including that of wingless, decapentaplegic and hedgehog, were normal in pattern and intensity compared with control discs (supplementary material Fig. S7; data not shown). Taken together with the defective proliferation observed in the larval CNS of ethanol-reared larvae, these data indicate that developmental ethanol exposure slows cell proliferation in the developing fly larvae, and this effect probably contributes to the ethanol-induced delay to eclosion and adult lethality.

Developmental ethanol exposure interferes with insulin signaling

Our observations that developmental ethanol exposure leads to reduced larval growth, delayed development, increased stored triglycerides (data not shown), small imaginal discs and small adult flies – all of which are phenotypes that are also seen upon impaired insulin signaling (Garofalo, 2002; Rulifson et al., 2002) – suggested that ethanol rearing might interfere with the insulin signaling pathway. This interference could occur at several levels, such as ligand production and/or secretion, receptor expression, and signal transduction. To investigate whether developmental ethanol exposure interfered with Dilp production, we analyzed dilp2 transcript and protein levels by quantitative real-time (RT)-PCR (qPCR) and immunohistochemistry, respectively, in both ethanol-reared and unexposed control larvae. Expression of the dilp2 gene was downregulated upon developmental ethanol exposure by approximately 50% and 25% in the larval brain and in whole larvae, respectively (Fig. 4A). Additionally, ethanol-reared larvae showed reduced Dilp2 protein in the insulin producing cells (IPCs) of the larval brain (Fig. 4B-D). This reduction in dilp2 transcript and protein was not caused by the loss of Dilp-producing cells (as observed by the number of dilp2-lacZ-expressing cells) in ethanol-reared larvae (data not shown).

To examine whether the ethanol-induced reduction in dilp2 expression is causally related to ethanol toxicity, we tested whether increasing Dilp expression would rescue the developmental delay and reduced viability caused by developmental ethanol exposure. We used dilp2-GAL4, which drives GAL4 specifically in the IPCs, to induce expression of dilp2 and dilp5, normally expressed in the IPCs, as well as dilp6, the expression of which is found in the fat body and has been shown to act redundantly to the IPC-expressed Dilps (Gronke et al., 2010). Increasing expression of dilp5 and dilp6 ameliorated both the lethality and delay phenotypes associated with developmental ethanol exposure (Fig. 4E,F; supplementary material Fig. S8A,B), whereas overexpression of dilp2 did not rescue either phenotype (data not shown). However, the ethanol-induced developmental phenotypes were improved when dilp2 was expressed ubiquitously using armadillo-GAL4 (arm-GAL4) as a driver

**Fig. 4. Developmental ethanol exposure alters insulin levels.** (A) Developmental ethanol exposure reduces dilp2 expression in larval brain and whole larvae as quantified by qPCR. mRNA levels are expressed as fold difference relative to control larvae (Kruskal-Wallis test, n=3, *P<0.04). (B,C) Dilp2 is reduced in ethanol-reared wandering larvae. (B) Representative images of Dilp2 in control (B) and ethanol-reared (C) larvae. Arrows indicate IPCs. Asterisk shows the esophagus. (D) Quantification of Dilp2 in the IPCs (Student’s t-test, n=10-13, *P<0.001). (E) Larval expression of dilp5 in IPCs of the CNS, using dilp2-GAL4, ameliorates the developmental delay and lethality induced by developmental ethanol exposure. Total eclosion (mean ± s.e.m.) of dilp5-overexpressing larvae (dilp2-GAL4/+; UAS-dilp5+/+) differs from control larvae (dilp2-GAL4/+ and UAS-dilp5/+) (one-way ANOVA, with Tukey HSD post-hoc analysis, n=6, *P<0.045). (F) Cumulative eclosion rates of dilp5-overexpressing larvae differs from control larvae (repeated measures ANOVA, n=6, between groups *P=0.0134, within groups *P=0.001). Time to 50% total eclosion (indicated by arrowheads) differs between dilp5-overexpressing larvae and control larvae (Dunnett’s, n=6, *P<0.001). n corresponds to the number of vials, containing 100 animals each.
Ethanol-reared flies exhibit developmental and behavioral defects

(supplementary material Fig. S8C,D). Taken together, these experiments show that increasing Dilp expression, specifically dilp5 and dilp6, in brain IPCs is sufficient to ameliorate the lethality and delay phenotypes induced by developmental ethanol exposure. Interestingly, expression of dilp2 lessened the ethanol-induced developmental phenotypes, but only when expression was driven throughout the animal. It is possible that expression of dilp2, unlike dilp5 or dilp6, is needed in the imaginal discs for efficient rescue of ethanol-induced toxicity (see Discussion). Increasing Dilp expression in flies that were reared on regular media did not alter adult viability or developmental time to eclosion (supplementary material Fig. S9), indicating that the rescue we observed in ethanol-reared animals was not due to general developmental differences. Together, these data show that developmental ethanol exposure impairs larval growth and decreases adult viability by interfering with Dilp production in the developing brain and possibly other larval tissues.

To further explore the idea that ethanol rearing interferes with the insulin signaling pathway, we investigated whether InR expression was also altered by developmental ethanol exposure. We found that InR transcripts were reduced by 70% in the larval brain, but were normal in the whole larva upon ethanol rearing (Fig. 5A), implying that CNS InR expression is particularly sensitive to inhibition by ethanol. If the insulin signaling pathway was compromised by developmental ethanol exposure, then InR mutants should be particularly sensitive to developmental ethanol exposure. To address this possibility, we examined three InR mutant alleles: InR

CNS InR is particularly sensitive to inhibition by ethanol. When reared on 5%-ethanol food, we observed only a slight reduction in adult viability in the InR heterozygotes compared with controls (data not shown). However, rearing flies on 7.5% ethanol food reduced adult viability from 61% in controls to ~40% in InR heterozygotes (Fig. 5B). Ethanol rearing did not produce developmental delay in the InR mutants (data not shown), suggesting that more pronounced reductions in InR expression are needed for the manifestation of this phenotype. Importantly, InR heterozygotes reared on regular media showed no differences in development time or adult viability compared with controls (supplementary material Fig. S10).

Taken together, our data leads us to propose that developmental ethanol exposure in flies inhibits the insulin signaling pathway by inhibiting both ligand and receptor expression, and that this inhibition is responsible for the developmental delay and reduced viability seen in ethanol-reared flies. Our data also suggest that the CNS InR is particularly sensitive to inhibition by ethanol.

Altered insulin signaling is responsible for ethanol-induced neurobehavioral changes

Perturbations of insulin signaling in the nervous system can lead to changes in sensitivity to ethanol-induced sedation (Corl et al., 2005). We therefore hypothesized that the reduction in Dilp-InR signaling during development might be responsible for the persistent neurobehavioral changes observed in ethanol-reared flies. To test this, we expressed UAS-dilp2 and UAS-dilp6 under the control of dilp2-GAL4 in larvae grown on 5% ethanol, and tested the resultant adults for sedation resistance and tolerance. Consistent with data obtained with wB flies, this developmental exposure led to increased resistance to sedation and a reduced ability to develop tolerance in the genetic control flies (Fig. 6A). However, expression of either dilp2 or dilp6 restored normal sensitivity to ethanol-induced sedation in flies reared on 5% ethanol, indicating a complete rescue of this phenotype by transgenic Dilp expression (Fig. 6A; supplementary material Fig. S11A). In addition, increasing expression of dilp2 (but not dilp6; supplementary material Fig. S11B) restored normal ethanol tolerance to ethanol-reared flies (Fig. 6B). Thus, the observed reduction in insulin signaling in flies reared on ethanol seems to be responsible for both the sedation resistance and tolerance development phenotypes. Interestingly, as for the rescue of the

Fig. 5. Developmental ethanol exposure reduces InR expression and InR mutants are sensitive to developmental ethanol toxicity.

(A) Developmental ethanol exposure reduces InR expression specifically in the larval brain. mRNA levels are expressed as fold difference relative to control larvae (Kruskal-Wallis test, n=3, *P=0.0369). (B) Heterozygous mutants for InR are sensitive to the decrease in eclosion induced by developmental ethanol exposure (Dunnett’s, n=6, *P<0.001).

Fig. 6. dilp2 expression rescues both sedation resistance and tolerance development. (A) dilp2 expression rescues ethanol-induced sedation resistance. Data are presented as difference in time to 50% sedation (ST50) for ethanol-reared flies as compared with control flies of the same genotype. dilp2-GAL4/UAS-dilp2 flies do not display increased sedation resistance upon ethanol-rearing, whereas both genetic background controls show the expected increase in ST50 (one-way ANOVA with Tukey HSD post-hoc analysis, n=12, *P<0.01). (B) dilp2 expression rescues ethanol-induced tolerance defects. Data are presented as the percent control tolerance (tolerance developed by ethanol-reared flies divided by tolerance developed by control flies of the same genotype multiplied by 100). Although both genetic background controls show a 40-50% reduction in tolerance when reared in ethanol, dilp2-GAL4/UAS-dilp2 flies develop normal levels of ethanol tolerance (one-way ANOVA with Tukey HSD post-hoc analysis, n=6, *P<0.05).
developmental phenotypes, there are differences in the effectiveness of different Dilps in restoring normal behavior to ethanol-reared flies.

**DISCUSSION**

**A Drosophila model of FAS**

Prenatal alcohol exposure can cause FAS, a complex disorder with numerous developmental, morphological and neurological deficits (Jones and Smith, 1973). In this study, we investigated the effects of developmental ethanol exposure in the fruit fly *Drosophila melanogaster*, and found many features in common with FAS. Flies reared on ethanol-containing food displayed a dose-dependent developmental delay, a small larval CNS, increased developmental mortality and reduced adult size. Developmental ethanol exposure also altered ethanol-responsive behaviors in adult flies. Ethanol-reared flies were hypersensitive to the stimulating effects of ethanol, abnormally resistant to ethanol-induced sedation, and defective in tolerance development, all phenotypes also observed in mammalian FAS models.

The phenotypic similarities between our model and mammalian FAS models extend to the specificity of critical periods for ethanol-induced developmental phenotypes. We found that, with the exception of ethanol-induced lethality, all of the phenotypes examined exhibit discrete critical periods. The critical period for ethanol-induced growth delay is during the second and third larval instars. Increased sedation resistance results from exposure during the second larval instar, whereas the tolerance defect maps to the late-third-instar or early-pupal stage. Of all the phenotypes examined, only the ethanol-induced lethality is cumulative, increasing in severity with longer exposure times. As with developmental ethanol studies in other organisms, these data indicate that the critical periods of ethanol sensitivity vary depending on what is being measured, i.e. viability versus developmental delay (Blader and Strahle, 1998; Oxendine et al., 2006). Such differences undoubtedly reflect the effects of ethanol on specific developmental events or processes. For example, in the case of the ethanol-induced growth delay, the critical period is a time of rapid cell division and growth in the larva. Our investigations show that ethanol exposure during this growth period interferes with cell division in the brain and imaginal discs (Fig. 3; supplementary material Fig. S7). Therefore, one explanation for the observed phenotypes is that insufficient cellular proliferation leads to delayed growth. Indeed, it is known that reduced cell proliferation in the imaginal discs can cause developmental delay (Brogiolo et al., 2001; Stieper et al., 2008). Taken together, these data suggest that reduction in imaginal disc size explains the ethanol-induced developmental delay.

The ethanol-induced defect in tolerance development is particularly interesting, because, unlike the other phenotypes examined, its critical period (late third instar to pupation) is during periods of neuronal differentiation, outgrowth and remodeling, rather than intense cell division. This might indicate that normal development of tolerance is dependent on neurite outgrowth and axon targeting, both of which depend on insulin signaling (Scolnick et al., 2008; Song et al., 2003).

Insulin signaling is reduced in flies reared in ethanol

Our studies show that, as in mammals, developmental ethanol exposure in flies leads to diminished insulin signaling. Expression of *dilp2* and *InR* was reduced in the brains of larvae reared on ethanol, and the growth and viability phenotypes were rescued by transgenic supplementation with several Dilps. Similarly, Dilp overexpression rescued the sedation sensitivity and tolerance defects of adult flies subjected to developmental ethanol exposure. It is interesting to note that ubiquitous overexpression of *dilp2* was required to rescue viability and developmental delay, whereas overexpression of *dilp2* in the brain rescued only the adult behavioral phenotypes of ethanol-reared animals. By contrast, expression of *dilp6* in the brain (driven by *dilp2*-GAL4) was sufficient to rescue both the growth and viability defects, as well as sedation resistance. Although it is possible that the differences are a result of lower expression of the *UAS-dilp2* transgene relative to *UAS-dilp6*, we consider this possibility unlikely because previous studies have found that overexpression of *UAS-dilp2* is more effective than *UAS-dilp6* to drive increased body size (Ikeya et al., 2002). These results might therefore reveal a previously unidentified specificity of function for *dilp2* in regulating behavior when expressed in the brain. Alternatively, it is possible that *dilp2* is less efficiently transported from the CNS to other tissues or has lower affinity for InR, such that CNS-specific expression is insufficient to rescue the imaginal-disc-mediated growth and viability defects.

Although our results with manipulations of the insulin pathway are satisfying as validation of our model system, they also suggest a potential mechanism for the adult behavioral phenotypes caused by developmental ethanol exposure. In the *Drosophila* eye, InR is required for proper photoreceptor axon guidance (Song et al., 2003). Similarly, IGF-I is a chemoattractant for axon growth cones in cultured rodent neurons, and IGF signaling is required for proper targeting of axons in the rodent olfactory bulb (Scolnick et al., 2008). It is reasonable to hypothesize that some or all of the behavioral defects caused by developmental ethanol exposure (and that are rescued by Dilp supplementation) are a result of improper neurite outgrowth and/or axon targeting during development. In *Drosophila*, it is possible to test this hypothesis in a relatively straightforward manner. For example, developmental exposure to ethanol results in increased ethanol-induced locomotion. It is known that a specific pair of dopaminergic neurons in the fly brain mediates ethanol-induced hyperactivity (Kong et al., 2010); similarly, neurons in the pars intercerebralis and central complex have been implicated in sensitivity to ethanol-induced sedation (Rodan et al., 2002). We will be able to examine the general organization of these brain regions using GFP driven by specific GAL4 lines. Analysis of detailed axon pathfinding could then be focused to the relevant neurons using the MARCM technique (Lee and Luo, 2001). We can therefore use this model to investigate the requirement for insulin signaling in the development of the nervous system and how it impacts adult behavior.

**Potential significance for FAS**

Our results in *Drosophila* and those of McGough and colleagues in rats (McGough et al., 2009) demonstrate that some of the deleterious effects of developmental ethanol exposure can be ameliorated by replacing lost insulin signaling. These results are important because they illustrate the potential for pharmacological intervention in FAS.

Despite decades of public awareness campaigns and widespread understanding that alcohol consumption during pregnancy can result in birth defects, the rate of alcohol abuse during pregnancy...
remains unchanged (Sampson et al., 1997). This is probably due in large part to the addictive effects of alcohol, and highlights the need for alternative solutions to the problem of prenatal ethanol exposure.

It is clear from human epidemiological data that genetic factors can modulate the teratogenic effects of alcohol. Monozygotic twins from alcohol-abusing mothers display concordance for FAS defects, whereas dizygotic twins do not (Christoffel and Salafsky, 1975; Streissguth and Dehaene, 1993). Moreover, different inbred mouse and chick strains, in which the timing of alcohol administration and blood alcohol concentration was controlled for, differ in their susceptibilities to ethanol teratogenesis (Boehm et al., 1997; Bupp Becker et al., 1998; Su et al., 2001). It is likely that many genes, in addition to those involved in insulin signaling, confer risk or protection from alcohol injury, yet none have been conclusively identified. Furthermore, insulin supplementation does not rescue the learning and memory defects of the disease, which are the most devastating symptoms of FAS (McGough et al., 2009), indicating the existence of other important developmental targets of ethanol.

The molecular identification of genetic factors that influence developmental ethanol toxicity has been hindered largely by the difficulty of performing unbiased, forward genetic screens in vertebrate systems, and it is here that our model is most useful. Our demonstration of both phenotypic and molecular conservation of developmental ethanol effects between flies and mammals indicates that Drosophila is a good model for further elucidation of the mechanisms of action of developmental ethanol exposure. This, in turn, will allow the identification of novel pharmacological targets to prevent/ameliorate the development of FAS.

METHODS

Drosophila strains and culture

Flies were raised at 25°C and 70% relative humidity on standard cornmeal/molasses medium. All experiments were carried out in a wB genetic background. The UAS-Dilp2 and dilp2-GAL4 strains were kindly provided by Ernst Hafen (IMSB, Zurich, Switzerland) and Eric Rulifson (UCSF, San Francisco, CA), respectively. The InR alleles were gifts from Marc Tatar (UCD, Davis, CA). All behavioral assays used 20-25 male flies aged 2-4 days after eclosion at the start of the experiment. Flies analyzed for behavior were subjected to brief (<5 minutes) CO₂ anesthesia no less than 24 hours before behavioral assays.

Developmental ethanol exposure

Egg collections were taken for 2-3 hours on Petri dishes containing 0, 5, 10 and 12% ethanol food. After 24 hours of development, 100 newly hatched larvae were transferred to vials containing either ethanol food or control food, and placed in a 5% ethanol bath (experimental conditions) or water bath (control conditions). The ethanol bath ensures that developing animals are exposed to ethanol during their entire development, which continues for another 10-16 days. The number of newly eclosed adult flies was counted daily between 9-16 days AEL (or 9-14 days AEL), and these data were used to generate cumulative eclosion rate plots, a direct measurement of egg-to-adult survival, and the time to 50% of total eclosion.

To determine critical periods for ethanol toxicity, larvae were collected from control food plates as they reached the desired developmental stage (first, second, or third larval instar), transferred to 5%-ethanol-containing food (or control food) and grown as described above. Survival and development time were calculated as described above, and newly eclosed adult flies were collected and subjected to behavioral experiments as described below.

Behavioral assays

All behavioral assays were performed in the locomotor tracking system (Wolf et al., 2002). Sedation sensitivity was quantified by exposing groups of 20-25 flies to an ethanol concentration of 100:50 (ethanol vapor: humidified air) (Corl et al., 2009; Rothenfluh et al., 2006). The number of flies having lost righting ability was counted at each time point. From these data, we calculated ST₅₀ (time to 50% sedation). Ethanol-induced locomotor activation was quantified by exposing groups of 20-25 flies to an ethanol concentration of 70:80 (ethanol vapor: humidified air) and analyzing their activity for a period of 30 minutes in 2- to 10-minute intervals.

qPCR

Control and ethanol-reared brains and whole larvae were snap frozen in liquid nitrogen and stored at ~80°C. Total RNA was extracted using TRIzol (GIBCO) according to the manufacturer’s instructions. mRNA in total RNA was reverse transcribed using TaqMan Reverse Transcription Reagents (Applied Biosystems) according to the manufacturer’s specifications. cDNA was analyzed by quantitative, real-time PCR using the ABI PRISM 7700 Sequence Detection System (Applied Biosystems). dilp2, InR and rp49 probe and primers (Dm01822534_g1, Dm02136224_g1 and Dm02151827_g1, respectively) were obtained from Applied Biosystems. rp49 transcript levels were used as an endogenous normalization control for RNA samples, and relative mRNA abundance was calculated using the comparative ΔCt method. Each sample was analyzed in triplicate. As negative controls, we used both no-template and DNase-treated non-reverse-transcribed mRNA samples; no significant amplification was observed in these samples.

BrdU labeling

Larvae were reared on 0% and 5% ethanol-containing food as described above, then placed on BrdU-containing food (0.7 mg/ml) for 4 hours during the first-to-second larval instar transition (24-28 hours AEL) or second-to-third larval instar transition (68-72 hours AEL). We chose the first-to-second larval instar transition because previous analysis showed that this early developmental stage was not delayed by developmental ethanol exposure and because all three neuroblast populations (mushroom body, optic lobe and thoracic) are actively cycling (Datta, 1995). The second-to-third instar transition can be identified by anterior spiracle morphology. After BrdU labeling, larvae were transferred back to 0%- or 5%-ethanol-containing food and brains were dissected from wandering larvae (larvae with half-empty gut). Brains were fixed for 30 minutes in 4% paraformaldehyde in PBS. Prior to incubation with anti-BrdU antibody, brains were incubated in 2N HCl for 1 hour, then neutralized three times for 5 minutes each in PBS with 0.1% Triton-X.

Immunostaining and imaging

Discs were fixed for 20 minutes in 4% paraformaldehyde in PBS. Larval brains were fixed for 30 minutes on ice in 4% paraformaldehyde in PBS. Rabbit anti-Dilp2 (Eric Rulifson) was
used at 1:500, mouse anti-BrdU (Becton Dickinson) was used at 1:100 and rabbit anti-β-galactosidase (Cappel) was used at 1:1000. Images were collected with Leica TCS SP2 confocal laser scanning microscope.

To ensure consistency of Dilp2 staining in controls and ethanol-reared larvae, immunostaining was performed in parallel and aliquots from the same primary and secondary antibody dilutions were used. Dilp2 levels in the IPCs of the CNS were measured using projection confocal images (as seen in Fig. 4B) and ImageJ. Briefly, IPCs from ethanol-reared and control larvae were outlined and then pixel intensity was measured.

The size of brain lobes from ethanol-reared (5% and 10% ethanol) and control larvae were measured using projection confocal images (as seen in Fig. 3A-C) and ImageJ. wB brain lobes were used as a normalization control, and relative brain lobe size in the ethanol-reared larvae was calculated.

Clonal induction and cell doubling time
Because ethanol exposure causes a developmental delay, cell clones were induced at the second-to-third instar transition, a developmental stage distinguished by anterior spiracle morphology. Larvae of the genotype y,w,his-flp22;Act5c>CD2-GALA, UAS-GFP were heat shocked for 15 minutes at 37°C at 72 hours AEL (or its equivalent in ethanol-reared larvae, which was ~84 hours AEL). Discs were dissected and fixed 48 hours later. The number of cells per clone was counted on a Leica TCS SP2 confocal laser scanning microscope and cell doubling times were calculated with the following formula: (log2)(hour)/logN, where N=cell number per clone and hour=age of clones.

TUNEL assay
TUNEL assay was performed using the In Situ Cell Detection Kit, TMR red (Roche). Larval brains were fixed at 4°C for 30 minutes in 4% paraformaldehyde in PBS. Brains were then permeabilized in 0.1 M sodium citrate for 1 hour, followed by treatment with 5 g/ml proteinase K in PBS for 2 minutes. Brains were washed twice in PBS then incubated in TUNEL labeling solution for 1 hour at 37°C. Brains were washed three times with PBS then mounted in Fluormount mounting media.

Ethanol absorption assay
Internal ethanol concentration was measured in extracts from 0%- and 5%-ethanol-reared animals at distinct developmental stages (first-, second- and third-instar larvae, pupae, and adults). Animals were frozen at the indicated developmental stages then assayed for ethanol content using a colorimetric enzymatic kit (Diagnostic Chemicals) (Moore et al., 1998). In order to calculate the internal ethanol concentration (millimolar) of 0%- and 5%-ethanol-reared larvae, pupae and adult flies, their volumes were measured. Animal volume was measured by placing 25-100 animals, of the desired developmental stage, into graduated Eppendorf tubes on ice. Then, 500 l of 100% ethanol was added to the tubes. The amount of displaced liquid (animal volume) was determined by removing ethanol, by Pipetman, until the meniscus read 500 l. The calculations of internal ethanol concentration (millimolar) in larvae, pupae and adults, presented in supplementary material Figs S3 and S4, used the average value of these volume measurements (see supplementary material Table S1).

TRANSLATIONAL IMPACT

Clinical issue
Consumption of alcohol during pregnancy can cause a complex disorder that is commonly known as fetal alcohol syndrome (FAS). Individuals with FAS exhibit a variety of symptoms, including persistent growth deficiencies, birth defects and mental retardation. Ethanol exposure is especially damaging to the developing nervous system and this has long-term consequences on adult behavior. The toxicity of developmental ethanol exposure has been attributed to numerous mechanisms, including ethanol metabolism and related oxidative stress, neuronal cell loss, and inhibition of growth factors and/or their signal transduction pathways. Although human epidemiological data and studies of animal models indicate that genetic factors confer risk for and protection from FAS, no genes that alter susceptibility to the syndrome have been conclusively identified.

Despite growing awareness of the dangers of drinking during pregnancy, the worldwide prevalence of FAS remains steady, at one to three per 1000 births. The high frequency of FAS coupled with the failure of public awareness programs highlights the need to understand more about the molecular basis of FAS, and to develop novel treatments to mitigate the complications of gestational ethanol exposure.

Results
To establish Drosophila as a genetic model for the study of FAS, the authors rear flies in the presence of ethanol and investigate the developmental and behavioral consequences of this exposure. Ethanol-reared flies show several phenotypes that are common to FAS, including reduced viability, developmental delay and small adult body size. Additionally, developmental ethanol exposure significantly impairs cell proliferation in the larval brain and imaginal discs. Finally, ethanol-reared flies exhibit persistent behavioral changes. These developmental and behavioral defects are found to be due largely to a reduction in Drosophila insulin-like peptide and insulin receptor expression.

Implications and future directions
This study demonstrates that Drosophila is a useful animal model for the study of the genetic and molecular mechanisms underlying the toxic effects of developmental ethanol exposure. The finding that, as in mammals, developmental ethanol exposure in flies leads to reduced insulin signaling might have important implications for understanding the cellular mechanisms underlying the behavioral problems associated with FAS in humans. In flies and mammals, insulin and insulin-like growth factors are known to be involved in axon guidance, neurite outgrowth and synaptogenesis. It is therefore possible that some of the behavioral deficits associated with FAS are due to miswiring of the developing brain, rather than just the loss of neurons owing to cell death or reduced cell division. Drosophila is particularly powerful as a model system given the ability to rapidly identify molecules of interest through forward genetics. Follow-up studies will involve genetic and molecular screens to identify novel mechanisms that contribute to developmental ethanol toxicity. These approaches will aid in the understanding of neurodevelopmental pathways that are altered by exposure to ethanol, which, in turn, might lead to the identification of drug targets for therapeutic intervention of FAS in humans.

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Ethanol absorption of control and ethanol-reared adult flies was measured during exposure to vaporized ethanol at 0, 5, 15 and 30 minutes (110:40, vaporized ethanol: humidified air) (Moore et al., 1998).

Larval feeding assay
Larvae were reared on 0%- or 5%-ethanol food as described above. At the second-to-third instar transition (staged by spiracle
morphology) or the late-third-instar–wandering-larvae transition (staged by the presence of wandering larvae in the vial), larvae were taken out of the food and washed with distilled water. Approximately 1 ml of the 0% - 5% ethanol food was mixed with 0.1% Coomassie Brilliant Blue dye (Bio-Rad) and poured into Petri dishes. Groups of 25 control or ethanol-reared larvae were placed on these Petri dishes for either 15 or 30 minutes. After feeding, larvae were washed in distilled water, and frozen immediately in liquid nitrogen. Larvae were homogenized in 300 μl distilled water, then 100 μl of 50% ethanol was added to the tubes. The samples were centrifuged at 13 g for 10 minutes, and supernatants were placed in new tubes (the last step was repeated three to four times until supernatants were clear). For analysis, 200 μl of supernatant was placed in a 96-well plate and the OD at 633 nm read in a spectrophotometer. Six groups of 25 larvae per treatment were analyzed for each time point.

Lifespan

For lifespan analysis, flies were maintained in vials at a density of 25 flies per vial on standard cornmeal/molasses medium. Flies were transferred to new vials three times per week.

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COMPETING INTERESTS

All authors declare that they do not have any competing or financial interests.

AUTHOR CONTRIBUTIONS

K.D.M. and R.L.F. performed and analyzed experiments describing the developmental and adult behavioral phenotypes induced by ethanol exposure, respectively. U.H. helped with experimental design. All authors contributed to manuscript preparation.

SUPPLEMENTARY MATERIAL

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REFERENCES

RESEARCH ARTICLE

Ethanol-reared flies exhibit developmental and behavioral defects


Under-reporting of foetal alcohol spectrum disorders: an analysis of hospital episode statistics

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Abstract

Background: Internationally, 0.97 per 1,000 live births are affected by foetal alcohol syndrome (FAS). However, prevalence intelligence has been limited in the UK, hindering the development of appropriate services. This analysis compares hospital admissions over time, between regions and with alcohol-related admissions for adult females to assess whether established patterns (such as the North experiencing elevated harms) can be identified.

Methods: A retrospective analysis of hospital admissions data (April 2002 to March 2008) for foetal alcohol spectrum disorder (FASD)-related conditions: foetal alcohol syndrome (dysmorphic) (n = 457); foetus and newborn affected by maternal use of alcohol (n = 157); maternal care for (suspected) damage to foetus from alcohol (n = 285); and 322,161 women admitted due to alcohol-related conditions.

Results: Whilst the rate of admission for alcohol-related conditions in women aged 15-44 years increased significantly by 41% between 2002/03 and 2007/08 (p < 0.0001), no such increases were seen in the numbers of FASD-related conditions (all p < 0.05). Established regional rates of admission for alcohol-related conditions in women aged 15-44 years old were not associated with admission for FASD-related conditions.

Conclusions: It would be expected that the North West and North East regions, known to have higher levels of alcohol harm would have higher levels of FASD-related conditions. However, this was not reflected in the incidence of such conditions, suggesting under-reporting. With incomplete datasets, intelligence systems are severely limited, hampering efforts to develop targeted interventions. Improvements to intelligence systems, practitioner awareness and screening are essential in tackling this.

Background

Worldwide estimates suggest that 0.97 per 1,000 live births are affected by foetal alcohol syndrome (FAS) [1], representing a significant cost to health services, with each affected baby estimated to cost a mean of $2,842 annually [2]. However, long-term costs may be much higher; FAS is associated with psychiatric problems, drug and alcohol addiction, memory and attention deficits [3,4], thus affecting a range of services including criminal justice, education as well as impacting on the family and local community. In the United Kingdom (UK), prevalence data are limited. Five UK studies contributed to the worldwide estimate; none identified FAS but they were restricted in sample size and geographic representation [1,5-10]. Subsequently, an analysis of Hospital Episode Statistics (HES) reported 128 cases in 2002/03 in England [3]. However, alcohol-related harm has since escalated [11,12].

Rates of alcohol related hospital admission for alcohol-related liver disease increased by over 100% between 1989/90 and 2002/03 in England and Wales [12]. Women are particularly at risk of alcohol-related harm due to biological and social factors [13-15]. For example, women are more likely to pre-load than men, a behaviour associated with higher risk of alcohol-related harm [15,16]. Such risk factors are of particular importance in the early stages of pregnancy, when the risks may be higher (the National Institute for Health and Clinical Excellence advises abstinence in the first three months) [17] and women are less likely to be aware of their pregnancy status. Levels of consumption are significant in young women, with one study in North West England showing that female nightlife users reported an average

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consumption of 16.5 units in one night, five times the recommended daily maximum of three units [18]. Even low levels of alcohol consumption, especially if consumed regularly, may affect health. Of women admitted to hospital for unspecified liver cirrhosis in England in 2005/06, 44.4% were estimated to drink from 0.1 to 2.4 units per day [19]. With no clear guidance on alcohol consumption in pregnancy and no established dose related threshold to distinguish between safe and harmful levels of consumption [3,20], pregnant women can be confused by advice around alcohol consumption [21], increasing the potential risk for alcohol misuse and the development of conditions such as FAS. However, without adequate monitoring of prevalence of these conditions, it is no possible to establish the true impact of consumption on unborn children in the UK.

We explore the reporting on foetal alcohol spectrum disorder (FASD) related disorder in England using HES. Hospital admissions were compared over time, between regions and with alcohol-related hospital admissions for adult females. We assess whether known geographical patterns in alcohol related harms (for example, whereby the North experiences elevated levels of alcohol-attributable hospital admissions and incapacity benefits claimants for alcoholism) [11] are reflected in FASD-related admission.

Methods
HES is a data warehouse containing details of all admissions to National Health Service (NHS) hospitals in England, as well as NHS funded inpatient care provided by independent treatment centres. Each record relates to an episode of care under a single consultant or medical team. Up to 20 diagnoses can be recorded for each episode (increasing from 14 in 2007/08). Diagnoses are coded using the International Classification of Diseases, 10th revision (ICD10). We used 4-digit ICD10 codes to identify inpatient episodes: O35.4, maternal care for (suspected) damage to foetus from alcohol; P04.3, foetus and newborn affected by maternal use of alcohol; and Q86.0, FAS (dysmorphic). Using HES for the UK financial years (April to March) 2002/03 to 2007/08, we identified episodes of care where any one of these diagnoses was recorded. Details extracted included: age at start of episode; sex; Government Office Region (GOR) of residence (from nine across England); and person identifier (HESID). The person identifier is a derived variable that links episodes of care to the same individual (based on NHS number and other identifiers), and which can be used to exclude repeat admissions for the same individual. Using the person identifier, we estimated the number of individuals who were admitted to hospital with each condition in each financial year. This measure combines incident and prevalent cases arising in a 12 month period, and allowed us to assess regional and temporal reporting trends in admission rates which were free from potential distortions arising from multiple hospital episodes in the same individual.

For admissions for foetus and newborn affected by maternal use of alcohol (ICD10 P04.3), we calculated rates using the number of live births in the relevant year as the denominator [22]. Live births were also used as the denominator for admission rates for maternal care for (suspected) damage to foetus from alcohol (O35.4). For FAS (Q86.0), since a diagnosis is often not made until later in childhood [3,23], we calculated hospital admission rates for children aged up to 14 years, and used mid-year population estimates for children aged up to 14 years as denominators. Here, we excluded 50 episodes involving patients aged 15 or over.

In addition, we used HES to estimate the number of women aged 15–44 years who were admitted to hospital with an alcohol-related diagnosis from 2002/03 to 2007/08. The methods used for this are described in detail elsewhere [19], but involve identifying numbers of individuals admitted with a range of alcohol-related conditions. For each condition, an alcohol-attributable fraction (AAF) was applied, which represents the proportion of cases where all alcohol cases are alcohol-related by definition and the AAF equals 1 (or 100%). It also includes conditions where alcohol is a contributory factor in only a proportion of cases, for example road traffic accidents (AAF: 0.09–0.21 for females aged 15–44 years), and cancers of the lip, oral cavity and pharynx (AAF: 0.35–0.40). Rates were calculated using mid-year population estimates for women aged 15–44 years as denominators. The rates provide a proxy measure of overall levels of alcohol-related harm in women of childbearing age, and can be compared with admission rates for FASD and related conditions in children.

HES also contains data for NHS outpatient appointments, and we examined the reporting of FASD-related conditions here for 2003/04 to 2007/08 [24]. However, because it is not mandatory for providers to code diagnoses on outpatient records, the completeness of the diagnosis fields is very low. Of 54 million outpatient appointments recorded in 2007/08, less than 3% of outpatient episodes have a valid diagnosis field [25], and we therefore predicted that these data would be unsuitable for assessing regional or temporal trends in FASD-related conditions. In fact, no cases were identified from the outpatient records and so no analysis was possible.

Trends in reporting over time and between regions were assessed using Poisson regression models, with likelihood ratio tests used to assess temporal and regional variation. We examined associations between regional admission rates for FASD-related conditions and alcohol-related harm in women of childbearing age.
using Pearson’s correlation coefficient. Analyses were performed using Stata 10. Ethical approval was not required [26], as secondary analysis of HES data can be used to identify public health issues and for general medical research under existing protocols. All analyses performed complied with these regulations [27].

**Results**

Between 2002/03 and 2007/08, there were 987 episodes with a diagnosis of FAS (ICD10 code Q86.0) involving 457 children aged under 15 years (Tables 1 and 2). Around 36% of children were aged under 1 at the time of admission (Table 2). The number of persons admitted increased substantially in 2006/07, relative to earlier years, and remained high in 2007/08. The overall trend was highly significant ($p = 0.0001$). Table 3 shows there were significant variations in regional rates ($p < 0.0001$ for heterogeneity). The North West had the highest rate of admissions at 1.67 (95%CIs: 1.39-1.99) per 100,000 population, while the lowest rates were seen in the North East (0.41 per 100,000; 95%CIs: 0.21-0.74).

There were 356 episodes with a diagnosis of foetus and newborn affected by maternal use of alcohol (ICD10: P04.3) between 2002/03 and 2007/08, involving 285 individuals (Tables 1 and 2). Nearly all (99%) were aged under one year when admitted (Table 2). The number of persons admitted increased by 59%, from 32 in 2002/03 to 51 in 2007/08, but this trend was not statistically significant ($p = 0.22$). The rate of admissions varied significantly ($p = 0.025$) between regions, ranging from 1.8 per 100,000 live births in London (95%CIs: 0.4-5.2) to 5.8 per 100,000 live births in the East Midlands (95%CIs: 3.4-9.3; Table 3). However, the region of residence was missing for 47% of the patients, so that the overall rate for England was higher than any of the regional rates at 7.8 per 100,000 live births (95%CIs: 6.9-8.7).

There were 184 episodes of maternal care for (suspected) damage to the foetus from alcohol (ICD10: O35.4) in England, involving 157 individuals (Tables 1 and 2). A quarter were women aged 15-24 years and the remainder were over 24 years. The number of persons admitted between 2002/03 and 2007/08 increased by 63% from 19 in 2002/03 to 31 in 2007/08 but the overall trend was not statistically significant ($p = 0.16$). There was significant regional variation in rates ($p = 0.0001$), ranging from 1.7 per 100,000 live births in London (95%CIs: 0.9-3.0) to 7.2 in the East Midlands and South West (Table 3).

Admission rates for alcohol related conditions in women aged 15-44 increased by 41% between 2002/03 and 2007/08 from 418 to 591 per 100,000. This increase was highly significant ($p < 0.0001$). Admission rates ranged from 757 [747-767] per 100,000 women aged 15-44 years in the North East regions to 375 [372-379] per 100,000 in London (Table 3). There was no significant correlation between the regional admission rates for alcohol-related harm in women and admissions for the three alcohol-related diagnoses involving children or pregnant women.

**Discussion**

It is extremely difficult to accurately estimate the prevalence of disorders such as FASD. There is uncertainty as to the level of maternal alcohol consumption that can cause FASD-related damage [4], and it can be difficult to obtain a valid understanding of consumption during pregnancy [28] as alcohol consumption amongst pregnant women is a highly sensitive area. In fact, experts in the United States of America suggest that the stigma

<table>
<thead>
<tr>
<th>Table 1 Trends in Hospital Episode Statistics for foetal alcohol spectrum disorder and related conditions, in residents of England 2002/03 to 2007/08</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Financial year</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>2002/03</td>
</tr>
<tr>
<td>2003/04</td>
</tr>
<tr>
<td>2004/05</td>
</tr>
<tr>
<td>2005/06</td>
</tr>
<tr>
<td>2006/07</td>
</tr>
<tr>
<td>2007/08</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

* The Hospital Episodes Statistics identification (HESID) field was used to link episodes relating to the same individual within a given year.
** The UK financial year runs from April to March.
*** A test of linear trend was obtained using likelihood ratio tests from Poisson regression models for rates based on number of individuals admitted.
Table 2 Hospital Episode Statistics for foetal alcohol spectrum disorder and related conditions, in residents of England 2002/03 to 2007/08 by person admitted*

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Q86.0: Foetal alcohol syndrome (dysmorphic), children aged under 15 years</th>
<th>P04.3: Foetus and newborn affected by maternal use of alcohol</th>
<th>O35.4: Maternal care for (suspected) damage to foetus from alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>104</td>
<td>22.8</td>
<td>278</td>
</tr>
<tr>
<td>2-11 months</td>
<td>62</td>
<td>13.6</td>
<td>4</td>
</tr>
<tr>
<td>1-4 years</td>
<td>155</td>
<td>33.9</td>
<td>1</td>
</tr>
<tr>
<td>5-14 years</td>
<td>136</td>
<td>29.8</td>
<td>0</td>
</tr>
<tr>
<td>15-24 years</td>
<td>N/A</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>25-44 years</td>
<td>N/A</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Not known</td>
<td>1</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

| Sex                     |   |   |   |   |   |   |
|-------------------------|   |   |   |   |   |   |
| Male                    | 235 | 51.4 | 145 | 50.9 | N/A | N/A |
| Female                  | 222 | 48.6 | 139 | 48.8 | 157 | 100 |
| Not known               | 1 | 0.4 |   |   |   |   |

| Total**                 | 457 | 100 | 285 | 100 | 157 | 100 |

*The Hospital Episodes Statistics identification (HESID) field was used to exclude repeat episodes relating to the same individual within a given financial year (running April to March). **Percentages may not sum to 100% due to rounding.

Table 3 Reporting rates for foetal alcohol spectrum disorder and related conditions, and hospital admission rates for alcohol related conditions in women aged 15-44 years, England 2002/03 to 2007/08 (by person admitted*)

<table>
<thead>
<tr>
<th>Government Office region of residence</th>
<th>Q86.0: Foetal alcohol syndrome (dysmorphic), children aged under 15 years</th>
<th>P04.3: Foetus and newborn affected by maternal use of alcohol</th>
<th>O35.4: Maternal care for (suspected) damage to foetus from alcohol</th>
<th>Women aged 15-44 years, admitted to hospital with alcohol related conditions**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Rate per 100,000 pop (95%CI)</td>
<td>n</td>
<td>Rate per 100,000 live births (95% CI)</td>
</tr>
<tr>
<td>North East</td>
<td>11</td>
<td>0.41 (0.21-0.74)</td>
<td>3</td>
<td>1.8 (0.4-5.2)</td>
</tr>
<tr>
<td>North West</td>
<td>125</td>
<td>1.67 (1.39-1.99)</td>
<td>21</td>
<td>4.3 (2.7-6.6)</td>
</tr>
<tr>
<td>Yorkshire and Humber</td>
<td>30</td>
<td>0.54 (0.37-0.77)</td>
<td>19</td>
<td>5.3 (3.2-8.2)</td>
</tr>
<tr>
<td>East Midlands</td>
<td>32</td>
<td>0.69 (0.47-0.98)</td>
<td>17</td>
<td>5.8 (3.4-9.3)</td>
</tr>
<tr>
<td>West Midlands</td>
<td>32</td>
<td>0.54 (0.37-0.76)</td>
<td>9</td>
<td>2.3 (1.0-4.3)</td>
</tr>
<tr>
<td>East of England</td>
<td>46</td>
<td>0.76 (0.56-1.01)</td>
<td>20</td>
<td>5.2 (3.1-8.0)</td>
</tr>
<tr>
<td>London</td>
<td>68</td>
<td>0.83 (0.65-1.06)</td>
<td>17</td>
<td>2.5 (1.4-3.9)</td>
</tr>
<tr>
<td>South East</td>
<td>41</td>
<td>0.46 (0.33-0.63)</td>
<td>27</td>
<td>4.8 (3.1-6.9)</td>
</tr>
<tr>
<td>South West</td>
<td>31</td>
<td>0.60 (0.41-0.85)</td>
<td>17</td>
<td>5.4 (3.1-8.6)</td>
</tr>
<tr>
<td>England***</td>
<td>457</td>
<td>0.84 (0.76-0.92)</td>
<td>285</td>
<td>7.8 (6.9-8.7)</td>
</tr>
</tbody>
</table>

| Correlation coefficient (p-value)****| 0.26 (0.50) | -0.26 (0.50) | -0.08 (0.83) |

*The Hospital Episodes Statistics identification (HESID) field was used to link episodes relating to the same individual within a given HES year (running April to March). **Percentages may not sum to 100% due to rounding. ***See Jones et al. (2008) for details of attributable fractions applied. ****Figures for England include reports where region of residence was not recorded, and so the numbers provided are not the sum of the regional numbers. *****Pearson’s correlation coefficient was used to assess correlations between the prevalence of alcohol related hospital admission (for women aged 15-44) and FAS or related conditions across regions.
attached to such disorders could reduce the likelihood of a diagnosis [28]. However, even without any associated stigma, diagnosis is difficult, not only due to the specialist training required [28,29] but also because affected individuals may have other diagnosable disorders or secondary disabilities [29], making it difficult to isolate FASD. Passive surveillance systems, such as HES used in this analysis, also present limitations. Intelligence may be restricted because systems rely on correct diagnosis by a large number of different medical practitioners [30]. Furthermore, trends in hospital data may be influenced by differential access and changes in service provision [31], as well as relying on individuals to have a reason to require hospital admission.

The HES data show an overall rate of hospital admission for FAS to be 0.84 per 100,000 population in England from 2002/03 to 2007/08. However, such figures cannot be used to measure prevalence as they can only capture intelligence on individuals admitted to hospital within a given year. Thus, other data collection methods (including clinical and epidemiological studies) produce higher incidence estimates, with worldwide estimates for FAS at 0.97 per 1,000 [1], and more recent estimates for Lazio (Italy) and mixed-racial, mixed socioeconomic populations in the United States of America at up to 7 per 1,000 [32,33]. Nevertheless, our findings highlight the limitations of current recording of FAS and FASD in England, and support the need for further development of the dataset if appropriate services are to be developed. Whilst the levels of alcohol-related harm including attributable hospital admission, mortality and crime have been increasing in recent years [11], no such increases were seen in any of the three diagnoses discussed here: FAS (Q86.0), maternal care for (suspected) damage to the foetus from alcohol (ICD10: O35.4) or foetus and newborn were affected by maternal use of alcohol. Because of the wide age range for children admitted with FAS (Q86.0), interpretation of temporal trends are more complicated for this condition. This is because to some extent the admissions will reflect maternal alcohol consumption patterns up to 15 years earlier, and for which we have no data. We found no evidence of an increase in admissions for FAS among children aged under 1 year, although numbers were admittedly very small, during a period when admissions for alcohol related harms in women of child-bearing age increased quite substantially.

We would predict that regional variations in alcohol-related hospital admissions in women of child-bearing age would be related to FASD diagnoses. Thus, it would be expected that the North West and North East regions, known to have higher levels of alcohol misuse and harm (evidenced by hospital admission data presented here as well as other harms including incapacity benefits claimants for alcoholism) [11] would have higher levels of FASD-related conditions. This was not found to be the case, strongly suggesting under-reporting of FASD-related conditions. The argument for under-reporting was strengthened through the outpatient data examined, where no episodes were revealed between 2003/04 and 2007/08 even though children with FASD-related conditions receive treatment as outpatients [3]. However routine outpatient dataset for England cannot provide any intelligence on this at present. Whereas treatment specialty is a mandatory reporting item for outpatient episodes, diagnosis and procedure codes are not [25]. As long as this remains the case, hospitals have little incentive to spend time and resources on reporting them, and hence the information is missing for the majority of records.

To understand the full extent of underreporting, an active ascertainment study is required [29]. The use of alcohol pregnancy screening tools (such as TACE or TWEEN) to identify high risk pregnancies is crucial here [3], although their validation in a UK setting is required. Screening could be performed by nurses, midwives and/or general practitioners, all of whom pregnant women are likely to encounter during their pregnancy. However, exposure to alcohol does not appear to have a direct correlation to outcome [4]. This means that, other than the most extreme cases, risk can be ascribed at birth or during pregnancy but it is not possible to provide a firm diagnosis. This is because difficulties often do not arise until later in life [3]. Without adequate screening or recording, if diagnosis cannot be made until later in life, complications can arise if crucial information has been lost, forgotten or become unavailable. To help address these issues, neonatal discharge summaries could include a section on high risk factors for later disorders including maternal alcohol consumption. This would follow the child and be accessible to them in later life, should such a diagnosis be sought. Finally the methods used to diagnose FASD are not consistent and there appears to be a lack of awareness as to the correct diagnostic framework. This could be addressed through improved training and more consistent use of diagnosis tools (such as the four digit code [3]) by community paediatricians, the most likely professionals to which these children will present to for diagnosis.

**Conclusions**

Current intelligence surrounding FASD-related disorders in England is severely limited. Data provided in this report serve to underline the existing gaps rather than present an understanding of the situation. If FASD-related disorders are to be effectively prevented, identified and treated, improvements to intelligence systems,
practitioner awareness and screening are essential. It is only by understanding incidence and characteristics of at-risk groups that effective services and interventions can be developed.

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Authors’ contributions
MM and KW developed the idea for the paper. MM, KW and DD wrote the manuscript. DD analysed the data. MM, KW, DD, PAC and MAB contributed to the data analysis. PAC, MAB and RM commented on and contributed to the drafting of the manuscript. MM is the guarantor. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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1. Students with social disabilities--Education (Elementary).
2. Children of prenatal alcohol abuse--Development.
3. Children of prenatal alcohol abuse--Education (Elementary).
4. Fetus--Effect of tobacco on.
5. Children of alcoholics--Education (Elementary).
7. Parents--Alcohol use.
8. Parents--Tobacco use.

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Executive Summary

Objective

The main purpose of the present study was to analyze longitudinal data from the “Better Beginnings, Better Futures” (BBBF) prospective study to examine relationships between prenatal exposure to alcohol and tobacco, separately and in combination, on developmental outcomes in young children from disadvantaged Ontario communities over the first four years of primary school (i.e. from 4 to 8 years of age). We also examined the effects of postnatal exposure to maternal drinking and smoking.

Four hypotheses were explored:

1. Children with higher-risk drinking mothers would show poorer developmental outcomes than those with lower-risk drinking mothers.

2. Children whose mothers smoked during pregnancy would show poorer developmental outcomes than those whose mothers did not smoke.

3. Children whose mothers were both high-risk drinkers and smokers during pregnancy would show the greatest developmental problems during primary school.

4. Maternal drinking and smoking during pregnancy would be more predictive of children’s primary school problem behaviours than postnatal exposure to parental drinking and smoking behaviour during the preschool years.

Methodology

Two sets of statistical analyses were used. First, analysis of covariance (ANCOVA) allowed us to determine whether prenatal exposure to alcohol and/or tobacco may have differential effects on various aspects of children’s functioning during the early primary school years. This first analysis was designed as a “proof-of-concept” or exploratory model. Measures in five domains of child development outcomes were analyzed in the ANCOVA analysis: general development, cognitive development/academic performance, social/emotional functioning, behaviour problems, and physical health.

Second, based on results from the ANCOVA, a more complex statistical technique (structural equation modelling [SEM]) was used to examine the pathways from prenatal and postnatal exposure to alcohol and tobacco, to parent and teacher reports of children's behaviour problems at age 8 (Grade 3). In this first-path analysis of this large and complex dataset, we focused on children’s externalizing (misbehaviour and problem behaviour) and internalizing (distress and emotion) behaviour problems in particular, because the latent trait structure of these behaviour problems was well enough documented in the research literature to use confirmatory techniques.

Both of the above-mentioned sets of analyses were carried out on the BBBF longitudinal dataset made up of over 400 children. These children and their families were recruited from disadvantaged Ontario communities at birth, and were followed prospectively at 33 and 48 months, and again at age 8. Thus, it was also possible to measure postnatal exposure to alcohol (i.e. maternal drinking) and tobacco (i.e. second-hand or environmental smoke), and to examine whether any negative effects of
prenatal exposure to alcohol and tobacco on children’s developmental outcomes increased or decreased over a four-year period between 4 and 8 years of age. Maternal alcohol use was assessed using the CAGE questionnaire (Ewing, 1984), while maternal tobacco use was assessed with questions from the National Longitudinal Survey of Children and Youth (NLSCY) and other population surveys. For all analyses, a comprehensive set of family socio-economic, cultural and demographic variables listed in Appendix 2 were employed as covariates in order to eliminate confounding effects of these variables.

Results

In the first ANCOVA analysis, children whose mothers reported higher-risk alcohol consumption during pregnancy showed long-term negative outcomes in measures of school performance and behaviour problems. These problems were accentuated in children whose mothers reported both alcohol and tobacco use during the pregnancy. However, negative outcomes were not evident in mothers who used only tobacco during pregnancy.

Further, the negative effects were more apparent at some times than at others: when children were 4 years of age, and faced with the challenges of formal school entry (i.e. poor school readiness) and again at 8 years of age, when individual differences in conceptual thinking may have been particularly salient to teachers. The percentage of measures demonstrating the disadvantage of children exposed to prenatal alcohol and tobacco increased from 37% at age 4 to 47% at age 8.

Second, results of the SEM suggest that the effects of the prenatal drinking and smoking were evident even when drinking and smoking behaviour at 33 months was taken into account. Although parental smoking behaviour (at age 33 months) predicted teacher reports of internalizing behaviour, prenatal maternal smoking accounted for both parent and teacher reports of externalizing problems and prenatal maternal drinking predicted teacher reports of both internalizing and externalizing problems.

Conclusions

Maternal drinking and tobacco use during pregnancy predicted that a child will have problems in elementary school, even when taking into account later smoking and drinking behaviour by the child’s parents. If these effects have endured for eight years, it seems unlikely that such effects will dissipate. If the trends are maintained as we expect, children’s academic and social behaviour may continue to be compromised into early adolescence. That is, prenatal exposure to maternal drinking and smoking may be linked to problems in or negative effects associated with cognitive and social development at critical periods in children’s development, with lifelong consequences.
1. Introduction

This secondary data analysis was commissioned by the Fetal Alcohol Spectrum Disorder Initiative, Public Health Agency of Canada. The data analyses used the Better Beginnings, Better Futures (BBBF) longitudinal database. The BBBF longitudinal study began in 1993. Over 500 children born in 1994 in six disadvantaged neighbourhoods across Ontario were recruited for the longitudinal study at birth; over 400 remained in the cohort at 8 years of age (Grade 3).

Children who are prenatally exposed to alcohol and tobacco have been found to be at risk for a range of adverse health and developmental outcomes from infancy into adulthood (Huizink & Mulder, 2006; Richter & Richter, 2001). The main purpose of the present study was to examine relationships between prenatal and postnatal exposure to alcohol and tobacco separately and in combination on developmental outcomes in young children over the first four years of primary school.

Measures in five domains of child development outcomes were analyzed, including general development, cognitive development/academic performance, social/emotional functioning, physical health, and externalizing and internalizing behaviour problems.

Two sets of analyses were used. First, analysis of covariance (ANCOVA) was used to determine whether prenatal exposure to alcohol and/or tobacco may have differential effects on these various aspects of children’s functioning during the early primary school years. Based on results from the ANCOVA, more complex statistical techniques (structural equation modelling [SEM]) were used to examine the pathways from prenatal and postnatal exposure to alcohol and tobacco smoke, to parent and teacher reports of children’s behaviour problems at age 8 (Grade 3). In this path analysis, we focused on externalizing and internalizing behaviour problems. Given the large array of variables available and the complexity of SEM, we needed to reduce the scope to make SEM feasible. We decided to begin with an array of 12 variables that allowed us to use existing research literature to develop a confirmatory model of the behaviour problem measures.

Four hypotheses were explored in this study:

1. Children with higher-risk drinking mothers would show poorer developmental outcomes than those with lower-risk drinking mothers.
2. Children whose mothers smoked during pregnancy would show poorer developmental outcomes than those whose mothers did not smoke.
3. Children whose mothers were both higher-risk drinkers and smokers during pregnancy would show the greatest developmental problems during primary school.
4. These prenatal effects would be evident even when taking into account more recent (i.e. postnatal) data on parental drinking and smoking collected when the child was 33 months old.
The BBBF longitudinal dataset was made up of over 400 children. These children and their families were recruited from disadvantaged Ontario communities at birth, and were followed prospectively at 33 and 48 months, and again at age 8. Thus, it was also possible to measure postnatal exposure to alcohol (i.e. maternal drinking) and tobacco (i.e. second-hand or environmental smoke), and to examine whether any negative effects of prenatal exposure to alcohol and tobacco on children’s developmental outcomes increased or decreased over a four-year period between 4 and 8 years of age.

Although previous studies have found evidence for an association between prenatal substance exposure and adverse effects on children’s development and functioning, many other studies have used clinical samples with very high prenatal substance exposure. In contrast, this is a large community-based sample of children who were followed prospectively from 3 months to 8 years of age. A strength of the prospective longitudinal study design is the ability to control for many familial and demographic factors.

Maternal alcohol use was assessed using the CAGE questionnaire (Ewing, 1984), while maternal tobacco use was assessed with questions from the National Longitudinal Survey of Children and Youth (NLSCY) and other population surveys.

Because associations between smoking during pregnancy and child outcomes may be due to more than just nicotine, for consistency, we use the term “prenatal tobacco exposure” in this report to refer to the effects on offspring of maternal smoking during pregnancy.

In the following section, we review some of the current research literature on the effects of prenatal exposure to alcohol and tobacco on children’s health.
2. Literature Review

Exposure to Prenatal and Postnatal Alcohol and Tobacco

2.1 Methodological Considerations

In discussing the associations between maternal substance use and children’s health, it is important to note at the outset several important caveats, summarized eloquently by Richter and Richter (2001), as well as Huizink and Mulder (2006). In this area of research, “gold standard” experimental designs (randomized controlled trials) are precluded because of obvious ethical concerns. Thus, the ability to draw causal conclusions is limited. Most research studies are based on cross-sectional designs with clinical samples – highly exposed children (sometimes termed “cases”) who are selected and compared to non-exposed children. In these types of studies, information on alcohol and smoking during pregnancy is collected retrospectively, up to 12 months or more after birth of the child. Use of a retrospective design increases the possibility of recall bias, wherein the mother is hesitant to admit substance use, or forgets the amount she consumed. A prospective longitudinal design is preferable, since the women are typically recruited during pregnancy and their child is followed for a long period (e.g. from 3 months to 8 years of age in the current BBBF longitudinal study).

A number of confounding factors can mediate the demonstrated associations between prenatal substance exposure and effects on children. These confounds may include, for example, socio-economic status (SES) and other demographic variables such as maternal education; prenatal nutrition, caffeine, drug use and psychological stress; prenatal medical care; and the postnatal environment such as exposure to second-hand smoke, quality of the parent–child interactions, and other familial risk factors. Two studies indicate that the association between prenatal tobacco exposure and effects on children may be influenced more by confounders than the association between prenatal alcohol exposure and effects on children (D’Onofrio et al., 2008; Sen & Swaminathan, 2007). Finally, it should be noted that the methods of assessment, specific outcome measures and level of substance use vary greatly among studies. Results from different studies, therefore, are not always directly comparable (Huizink & Mulder, 2006).

Nevertheles, the preponderance of evidence clearly points to strong associations between prenatal alcohol and tobacco exposure and adverse consequences on children’s physical, cognitive, social/emotional and behavioural development (Richter & Richter, 2001).
Although a relatively large body of literature has examined effects of prenatal exposure to alcohol and tobacco in newborns and infants, there are fewer studies on older children. Thus, in the sections below, we focus on effects on preschool and primary school-aged children.

- It is important to assess developmental outcomes in childhood since these outcomes predict health and well-being into adolescence and adulthood (Pihlakoski et al., 2006).

2.2 Alcohol Exposure in Prenatal and Postnatal Periods

In Canada, the rate of mothers who report drinking any alcohol during pregnancy is approximately 10.5%, according to the 2005 Canadian Community Health Survey (CCHS). In this nationally representative survey, women who had given birth in the previous five years were asked about their alcohol use during pregnancy. In the 2005 survey, the rate of alcohol use was slightly lower than in the previous two CCHS surveys: 12.4% of women in 2003 and 12.2% of women in 2000–01 reported drinking alcohol during pregnancy (Public Health Agency of Canada, 2008). In the CCHS, women over the age of 35 or between 15 and 19 years were generally more likely to report alcohol consumption than mothers between the ages of 20 and 34. Regionally, Quebec had the highest rate of maternal drinking during pregnancy in 2005 at 17.7%, and Newfoundland and Labrador had the lowest rate at 4.1%.

Slightly higher rates of maternal alcohol use during pregnancy were reported in the National Longitudinal Survey of Children and Youth (NLSCY) – in 2002–03, 15.6% of mothers reported consuming alcohol during their pregnancy and in 2000–01, 13.9% did so (Government of Canada, 2007).

A more in-depth analysis of the 2000–01 CCHS data from Alberta indicates that younger mothers (under 20 years) were more likely to binge drink (i.e. drink 5 or more drinks on one occasion) than mothers over 26 years of age. These analyses also indicate that higher-income pregnant women in Alberta were more likely to be drinkers; however, when they did drink, lower-income pregnant women were more likely to binge drink once per month or more.

These data are supported by the 2006–07 Maternity Experiences Survey results, which indicated that approximately 10.5% of women reported drinking during pregnancy. The Maternity Experiences Survey is a project of the Public Health Agency of Canada’s Canadian Perinatal Surveillance System and was conducted by Statistics Canada. The study surveyed women 15 years of age and older who had had a singleton birth in the three months prior to the 2006 Census (Public Health Agency of Canada, 2009).

These figures indicate that a substantial number of Canadian children will continue to be exposed to alcohol in the prenatal stage unless there are dramatic changes in maternal behaviour.
2.2.1 Heavy Drinking During Pregnancy and Fetal Alcohol Spectrum Disorder

Alcohol is established as a significant teratogen, and results in a host of cognitive, social and behavioural deficits such as impairments in general intellectual functioning, language and academic achievement; developmental delays; and problems with learning, memory, adaptive functioning, attention, inhibition, and state regulation (Bailey et al., 2004; Mattson, Riley, Gramling, Delis & Jones, 1998; Streissguth & O’Malley, 2000). The consequences of alcohol use in pregnancy range from subtle problems to the unique cluster of abnormalities that constitutes Fetal Alcohol Syndrome (FAS) – the most severe of the four conditions that comprise Fetal Alcohol Spectrum Disorder (FASD) (Chudley et al., 2005; Jacobson & Jacobson, 2002). FAS was first described in 1973 by Jones and Smith, and is caused by heavy drinking during pregnancy. A diagnosis of FAS requires evidence of four main features (growth deficiency, facial malformation, central nervous system damage and confirmed (or unconfirmed) prenatal alcohol exposure), although substantial developmental disabilities are also evident in children without facial malformation (Chudley et al., 2005). The term “FASD” refers collectively to a number of disabilities associated with prenatal exposure to alcohol. The three conditions in the spectrum, all permanent and preventable, include FAS, partial-FAS (pFAS), and alcohol-related neurodevelopmental disorder (ARND). The latter two terms are applied to children who have confirmed prenatal alcohol exposure and who exhibit some, but not all, of the FAS features (Chudley et al., 2005). In Canada, it is estimated that 9 out of 1,000 babies each year are born with FASD (Public Health Agency of Canada, 2007).

The majority of studies to date have focused on binge drinking during pregnancy and the associations with FAS among exposed children (Huizink & Mulder, 2006). Substantial evidence indicates that binge-like drinking patterns, in which the fetus is exposed to high blood alcohol concentrations over relatively short periods of time, are particularly harmful for offspring, and place the fetus at the highest risk of FASD (Maier & West, 2001). Binge drinking is often defined as 5 or more drinks on one occasion; one standard drink is equivalent to 0.5 oz. of absolute alcohol (AA) (Streissguth, Barr & Sampson, 1990). For example, Streissguth, Barr and Sampson (1990) reported that children whose mothers reported any binge drinking in the period prior to pregnancy recognition demonstrated poorer academic performance on reading and arithmetic at age 7 than children whose mothers abstained or did not binge drink during pregnancy.

Notwithstanding the profound negative effects of heavy drinking during pregnancy, a growing body of literature has documented adverse effects on children’s functioning at low to moderate levels of prenatal alcohol exposure (e.g. Jacobson & Jacobson, 1994; Sayal, Heron, Golding & Emond, 2007; Sood et al., 2001).

2.2.2 Moderate and Low Levels of Drinking During Pregnancy: Cognitive and Behavioural Outcomes

Recently, the effects of low levels of prenatal alcohol consumption have come under particular scrutiny. Controversial results from the U.K. Millennium Cohort study published online late in 2008 indicated that children born to mothers who drank up to 1 to 2 drinks per week or per occasion during pregnancy were not at increased risk of clinically relevant behavioural difficulties or cognitive deficits compared with children of abstinent mothers. The odds ratios in this study actually indicated lower risks of these problems at age 3 among children of light drinkers, even after controlling for possible confounds including socio-economic
factors, current drinking, mother’s mental health, and child–parent relationship (Kelly et al., 2009). This study has received much media attention and prompted several commentaries and debates among researchers and clinicians, some of whom listed numerous methodological limitations of Kelly and colleagues’ study (e.g. Gijsen, Fulga, Garcia-Bourmissen & Koren, 2008; Nathanson, Jayesinghe & Roycroft, 2007; Sayal, 2009).

Indeed, Kelly and colleagues’ (2009) results were surprising in light of a growing body of literature that has documented the adverse effects of low and moderate levels of prenatal alcohol on behaviour, IQ, learning, and other educational outcomes among early school-aged children (Jacobson & Jacobson, 1994; Jacobson, Chiodo, Sokol & Jacobson, 2002; Sayal, Heron, Golding & Emond, 2007; Sood et al., 2001).

For example, Sayal and colleagues (2007) reported an increased risk of behavioural and emotional problems (composite score of these problems) among girls whose mothers drank less than 1 drink per week during pregnancy. These effects were observed for parent ratings at age 47 months and 81 months, and were confirmed by later teacher ratings between 7 and 9 years of age. Similarly, in a prospective study of 501 mother-child pairs, Sood et al. (2001) reported that children with any prenatal exposure to alcohol were 3.2 times more likely to have delinquent behaviour scores in the clinical range. Other behavioural outcomes related to prenatal alcohol exposure include psychosocial deficits and problem behaviours, which have been found in FAS children and in children who were prenatally exposed to moderate levels of alcohol. These children were at increased risk of psychiatric disorders (Streissguth, Barr, Kogan & Bookstein, 1996) and were more likely to be rated as hyperactive, disruptive, impulsive or delinquent (Roebuck, Mattson & Riley, 1999).

The level of cognitive deficits among children with low–moderate prenatal alcohol exposure has not been studied extensively. Several studies, however, indicate that moderate alcohol exposure is associated with cognitive deficits in primary school-aged children, including IQ decrements, learning and memory problems and deficits in information-processing speed (Carmichael-Olson et al., 1997; Streissguth, 2007; Streissguth, Barr & Sampson, 1990; Wilford, Leech & Day, 2006). Streissguth, Barr and Sampson (1990), for example, found that moderate alcohol exposure (defined in this study as 2 or more drinks/day) was related to a 6-point decrease in IQ and lower reading and arithmetic achievement test scores at age 7, after adjustment for 15 covariates including prenatal tobacco exposure. In a prospective study of 636 mother-child pairs, Wilford, Leech and Day (2006) reported that moderate alcohol exposure (approximately 1 drink per day) during the first and second trimesters was related to decreases in composite IQ score as well as verbal, abstract/visual, and quantitative subscales at age 10 among African American children.

It appears that there may be dose–response effect of alcohol on child outcomes, wherein the heavier the level of maternal drinking during pregnancy, the greater the magnitude of negative effects on the exposed child (Goldschmidt, Richardson, Stoffer, Geva & Day, 1996; Jacobson and Jacobson, 2002; Jacobson, Jacobson, Sokol, Chiodo & Corobana, 2004; Sood et al., 2001). For example, Jacobson, Jacobson, Sokol, Chiodo and Corobana (2004) reported that each additional ounce of absolute alcohol (AA) per day (approximately 2 standard drinks) during pregnancy was related to a 2.9 point decrease in overall IQ at age 7.

In the section below, we examine the effects on externalizing and internalizing behaviour problems in particular.
2.2.3 Externalizing and Internalizing Behaviour Problems

An emerging literature has begun to document the associations between prenatal alcohol exposure and externalizing behaviour problems in school-aged children. Specifically, researchers have documented higher rates of inattentive, hyperactive, aggressive and antisocial behaviour in alcohol-exposed children compared with children with no exposure to alcohol (Brown et al., 1991; Mattson & Riley, 2000; Nanson & Hiscock, 1990; Sood et al., 2001).

In the aforementioned study by Sood et al. (2001), low levels of prenatal alcohol exposure (i.e. 1 alcoholic drink per week) were significantly associated with higher externalizing (aggressive and delinquent), internalizing (anxious/depressed and withdrawn), and other behaviour problems at 6 to 7 years of age. These results persisted even after careful control for confounding factors, including prenatal tobacco exposure, maternal age, education, marital status, SES and the home environment. Similarly, in a smaller sample of 88 Caucasian children 6 to 13 years old, heavy prenatal alcohol exposure (mothers were known to abuse alcohol, but children did not have diagnosis of FAS) was related to greater externalizing (attention, aggression, delinquency), internalizing (total score) and total behaviour problem scores (Mattson & Riley, 2000). In one retrospective study of children with FAS or fetal alcohol effects (FAE) (now part of the FASD) or children with attention deficit hyperactivity disorder (ADHD) and controls (Nanson and Hiscock, 1990), parents rated both groups of children as being more hyperactive and more inattentive than the children with no FAS and no ADHD.

Few studies have compared parent and teacher rating of externalizing problems. However, Brown et al. (1991), did compare these two groups of informants. Although teacher reports reflected more social competence problems, depression and externalizing behaviours in 5-year-old children whose mothers continued to drink during pregnancy compared with those whose mothers stopped drinking or who never drank, parent reports revealed no such differences (Brown et al., 1991).

Recently, researchers have also turned their attention to the associations between prenatal alcohol exposure and children’s internalizing problems such as depression and anxiety. O’Connor and colleagues have published a series of reports indicating associations between prenatal alcohol and childhood-onset depression (O’Connor & Kasari, 2000; O’Connor & Paley, 2006). For example, O’Connor and Paley (2006) used SEM to investigate the pathways from prenatal alcohol exposure to child depressive symptoms and the mediating effects of maternal and child characteristics, in a small sample of children aged 4 to 5 years. Results indicated that prenatal alcohol exposure was associated with more negative child affect. In turn, mothers of more negative children were less emotionally connected to their children, and those children had higher levels of depressive symptomatology. Interestingly, these results could not be explained by current maternal drinking patterns (O’Connor & Paley, 2006). Similarly, analyses from a large prospective sample of children prenatally exposed to moderate levels of alcohol indicated an association between higher rates of internalizing problems at age 10 and greater prenatal alcohol exposure, after controlling for significant covariates that also predicted problem behaviours (Day & Richardson, 2000).
2.2.4 Postnatal Alcohol Exposure

Both prenatal and postnatal alcohol exposure appear to shape children’s developmental trajectories (O’Connor & Paley, 2006). It is of importance, then, that prenatal alcohol use is strongly correlated with postnatal use (Carmichael-Olson, O’Connor & Fitzgerald, 2001). Such an association raises the possibility that there is some aspect of postnatal drinking that could account for effects attributed to prenatal drinking, and deserves to be addressed.

A large body of literature has examined the adverse effects of children of alcoholics (termed COAs). These studies suggest that children of alcoholics are at higher risk for a variety of emotional, behavioural and other developmental problems (Fitzgerald, Davies & Zucker, 2002). Despite the well-documented adverse effects of postnatal exposure to alcohol, several researchers have noted that the effects of maternal current drinking do not have much of an effect on the strong association between prenatal alcohol and internalizing behaviour problems (O’Connor & Paley, 2006), aggressive behaviour, or social competence of school-aged children (Brown et al., 1991). It is possible that prenatal alcohol exposure may have effects on behaviour problems and socio-emotional functioning that are independent of current maternal drinking, or that postnatal alcohol use must be at a relatively high level to significantly contribute to adverse effects on children (O’Connor & Paley, 2006).

2.3 Tobacco Exposure in the Prenatal and Postnatal Periods

In the 2005 Canadian Community Health Survey (CCHS), 13.4% of women reported smoking cigarettes during pregnancy, and 14.1% of women reported being exposed to second-hand (environmental) tobacco smoke during their pregnancy (Public Health Agency of Canada, 2008). These rates have decreased since the 2000–01 CCHS, when 17.7% of women reported smoking during pregnancy and 22.4% reported being exposed to second-hand smoke. Similar rates of smoking during pregnancy were observed in the National Longitudinal Survey of Children and Youth (NLSCY); in 2002/03, 15.9% of women reported smoking during pregnancy, and earlier in 2000/01, 18.5% reported this behaviour (Government of Canada, 2007). In the 2005 CCHS survey, younger mothers, and mothers with less than a high school education were more likely to report this behaviour. Regionally, in the 2005 CCHS, British Columbia and Ontario had the lowest rates of maternal smoking during pregnancy (9.7% and 10.3%, respectively); Nunavut and Northwest Territories had the highest rates (59.5% and 32.8%, respectively). Data from the NLSCY indicate that 35% of women who reported smoking during pregnancy smoked 10 or more cigarettes a day.

Unfortunately, it appears that the majority of smokers will continue this behaviour throughout their pregnancy. In the U.S. National Pregnancy and Health Study, approximately two-thirds of women who smoked prior to their pregnancy continued smoking into the last trimester (National Institute on Drug Abuse, 1996).
2.3.1 Level of Prenatal Tobacco Exposure Associated with Adverse Outcomes

- Research indicates a dose–response gradient, wherein the adverse effects on children exposed prenatally to tobacco (and its numerous by-products) is dependent on the frequency and quantity of maternal smoking during the gestation period (Richter & Richter, 2001). The greater the exposure, the more likely the child is to suffer. For example, birth weight decreases in direct proportion to the number of cigarettes smoked (Cornelius & Day, 2007).

- The timing of exposure also affects the outcomes in the exposed child, with the most pronounced effects of smoking on birth weight, for example, occurring during the third trimester (Richter & Richter, 2001).

Dose–response relationships have also been documented with other childhood outcomes, including cognitive and behavioural functioning (Huizink & Mulder, 2006; Martin, Dombrowski, Mullis, Wisenbaker & Huttenun, 2006). In a prospective longitudinal study of 676 Finnish children, Martin and colleagues (2006) classified maternal tobacco use during pregnancy as none, light (1–5 cigarettes/day) and heavy (6 or more cigarettes per day). At 12 years of age, children of light smokers exhibited levels of behaviour problems and academic achievement that were intermediate between those reported for non-smokers and for heavy smokers.

2.3.2 Effects on Growth, Cognitive and Behavioural Outcomes

A substantial body of literature has documented the adverse effects of maternal smoking during pregnancy on birth weight and infant growth (Cornelius & Day, 2007; Richter & Richter, 2001). Children born to mothers who smoke are also at risk of health conditions such as cleft palate, decreased lung function and middle ear disease; these effects are independent of the adverse health effects of environmental tobacco smoke (Richter & Richter, 2001).

A smaller literature base is available for effects of prenatal tobacco exposure beyond the neonatal and infant period. The available research does indicate relationships between prenatal tobacco exposure and childhood cognitive and behavioural developmental deficits, such as lower scores in general intellectual functioning, reduced verbal ability, increased activity, inattention and impulsivity, and higher rates of conduct disorder and other behaviour problems (Cornelius & Day, 2007; Huizink & Mulder, 2006; Richter & Richter, 2001).

In terms of cognitive outcomes, in the Ottawa Prenatal Prospective Study for example, tobacco exposure was significantly related to lower cognitive functioning and poorer language development at 2, 3 and 4 years of age (Fried & Watkinson, 1990; Fried, O’Connell & Watkinson, 1992). When those children were 9 to 12 years old, prenatal tobacco exposure was negatively associated with language and reading abilities. Similar results on cognitive functioning were reported by Milberger, Biederman, Faraone, Chen & Jones (1996) and Olds, Henderson and Tatelbaum (1994). In these three studies, associations between prenatal tobacco exposure and cognitive deficits remained significant after adjustment for confounds such as SES, education, marital status and parental IQ. However, none of the studies controlled for ongoing exposure to environmental tobacco smoke. Some researchers assert that associations between prenatal
tobacco exposure and cognitive development can be explained by differences in genetics or the home environment, such as postnatal exposure to second-hand smoke; this area is discussed in section 2.3.4 (D’Onofrio et al., 2008; Eskenazi & Trupin, 1995).

Although prenatal exposure to tobacco appears to influence cognitive functioning, a stronger association is apparent with children’s behaviour problems (D’Onofrio et al., 2008). For example, one 10-year longitudinal study reported that mothers who smoked frequently while pregnant were more than four times as likely as less frequent smokers or non-smokers to have sons who developed a conduct disorder, and were more than five times as likely to have daughters who became dependent on drugs (Weissman, Warner, Wickramaratne & Kandel, 1999). It appears that there are clear long-term adverse effects of prenatal tobacco exposure on behaviour, according to results from a New Zealand birth cohort study (Fergusson, Woodward & Horwood 1998). Fergusson and colleagues reported that children exposed, compared with those not exposed to maternal smoking during pregnancy, had higher symptom rates of chronic disease, substance abuse, and depression at 16 to 18 years of age. The effects remained after the authors controlled for socio-economic disadvantage, impaired child-rearing behaviour, and parental and family problems. The bulk of the literature on behavioural outcomes has focused on Attention Deficit Hyperactivity Disorder (ADHD) and other externalizing behaviours. We review some of these studies in the next section.

### 2.3.3 Externalizing and Internalizing Behaviour Problems

Smoking during pregnancy has been consistently linked with externalizing problems in childhood, especially in boys (e.g. Ashford, van Lier, Timmermans, Cuijpers & Koot, 2008; Martin, Dombrowski, Mullis, Wisenbaker & Huttenen, 2006; Wakschlag, Pickett, Cook, Benowitz & Leventhal, 2002; Williams et al., 1998). For example, prenatal exposure to tobacco (mother smoked 1 or more cigarette(s)/day) was related to significantly higher parent-rated activity levels at age 5 in a sample of 676 children from the Helsinki Longitudinal Project in Finland (Martin, Dombrowski, Mullis, Wisenbaker & Huttenen, 2006). Among the same sample at age 12, children who were prenatally exposed to tobacco were rated by their teachers as being more distractible and less mature than children who had no prenatal exposure to tobacco. Martin and colleagues controlled for a range of possible confounds, including SES, maternal age and maternal psychological distress but did not control for postnatal or environmental tobacco smoke exposure. In a population-based cohort of 1,452 twin pairs aged between 5 and 16 years from the Greater Manchester Twin Register, maternal prenatal smoking was found to have a statistically significant relationship with both parent and teacher ratings of ADHD, even after control for two sets of potential confounds – genetic factors and familial/environmental influences (Thapar et al., 2003). Linnet et al. (2003) found consistent evidence of independent effects of smoking on a variety of symptoms related to ADHD in 4- to 7-year-old children, after statistical control for factors known to confound the relationships with ADHD (e.g. familial psychopathology). In a sample of 4,879 children from an Australian longitudinal study, Williams et al. (1998) found a dose-response relationship between externalizing behaviour problems and maternal smoking during pregnancy at 5 years of age. Weaker relationships were evident for internalizing behaviour problems. The associations appeared to be independent of a wide range of possible confounds, such as SES, education, social class, marital status and mental health. Williams and colleagues concluded that these results are strongly suggestive of a causal relationship.
Unfortunately, none of the four studies described above appeared to statistically adjust for the effects of postnatal or environmental exposure to tobacco smoke. There remains disagreement in the literature about the importance of confounding factors on the relationship between prenatal tobacco exposure and child behaviour problems. For example, although Williams et al. (1998) concluded that the relationship is causal, Maughan, Taylor, Caspi and Moffitt (2004) asserted that the association between prenatal tobacco and conduct disorder may be better accounted for by confounds, including antisocial behaviour in both parents, depression in mother and family environment. D’Onofrio et al. (2008) agreed, suggesting that environmental and genetic factors account for the associations between prenatal tobacco exposure and externalizing problems.

Compared with the knowledge base for externalizing outcomes, the relationship between prenatal tobacco exposure and internalizing behaviours is less well documented. Results for these studies have been mixed. Weitzman, Gormaker and Sobol (1992) employed a sample of 2,256 children aged 4 to 11 years from the U.S. National Longitudinal Survey of Youth (NLSY). Three groups of children were compared: those whose mothers smoked both during and after pregnancy; those whose mothers smoked only during pregnancy; and those whose mothers smoked only after pregnancy. Weitzman et al. did not include a direct comparison with mothers who did not smoke at all, so results are less clear with respect to the unique influence of prenatal smoking. However, it was clear that children whose mothers smoked both during and after pregnancy had significantly increased levels of depression and anxiety compared with children whose mothers smoked only after or only during pregnancy. This association remained after adjusting for the child’s sex, birth weight, and various demographic and maternal characteristics. More recently, Ashford, van Lier, Timmermans, Cuijpers and Koot (2008) also used a longitudinal sample, and reported that prenatal tobacco exposure was a predictor of internalizing (and externalizing) behaviour problems in 396 children over the period of ages 5 to 18 years.

However, two studies have found that the effect of prenatal smoking on internalizing problems diminished after controlling for potentially confounding variables. For instance, the increased risk of internalizing problems among exposed children was found to disappear after controlling for variables such as socio-demographic factors, maternal anxiety and depression, birth weight, and pre- and perinatal complications (Williams et al., 1998) or after adjusting for socio-economic disadvantage, impaired child-rearing behaviours, and parental and family problems (Fergusson, Woodward & Horwood, 1998).

### 2.3.4 Postnatal Tobacco Exposure

Many women who smoke cigarettes during pregnancy continue to smoke after the pregnancy (Cornelius & Day, 2007). Children born to mothers who smoked during pregnancy are thus likely to continue to be exposed after the pregnancy. The most often cited consequence of postnatal exposure to environmental tobacco smoke (ETS) is an increased risk of sudden infant death syndrome (SIDS) (Cornelius & Day, 2007). Behavioural and cognitive outcomes, however, are also affected by postnatal exposure to ETS; however, results are mixed. For example, Cornelius, Goldschmidt, DeGenna and Day (2007) reported that environmental tobacco smoke was not a significant predictor of child behaviour at age 6 when prenatal tobacco exposure was considered. Weitzman, Gormaker and Sobol (1992), in contrast, reported a significant relationship between both prenatal and postnatal exposure and children’s behaviour problems, even after controlling for confounds such as child’s age, sex, family structure and income.
2.4 Effects of the Combination of Prenatal Alcohol and Tobacco

It is widely acknowledged that alcohol and tobacco use during pregnancy typically occur in combination (Cornelius & Day, 2007; Sen & Swaminathan, 2007). Specifically, research indicates that between 40% and 76% of women who report smoking during the first trimester of their pregnancy report concurrent alcohol use (Cornelius, Taylor, Geva & Day, 1995; Day, Cornelius & Goldschmidt, 1992; Streissguth, Barr & Sampson, 1990). Despite these statistics, few studies have assessed the effects of the interaction of both substances on the exposed child.

In the Ottawa Prenatal Prospective Study, among children aged 3 and 4 years, heavier maternal use of both alcohol and tobacco during pregnancy was related to statistically lower average scores for child comprehension and motor skills compared with groups reporting lighter use of the two substances (Fried, O’Connell & Watkinson, 1992; Fried & Watkinson, 1990). This effect was not evident at ages 5 and 6. Other reports have indicated that prenatal alcohol exposure has greater effects than prenatal tobacco. In analyses from the U.S. NLSY, Sen and Swaminathan (2007) examined the effects of both substances on children’s behaviour problems between 4 and 10 years of age. Results indicated that whereas prenatal alcohol exposure continued to have effects on behaviour problems after controlling for confounds, prenatal smoking largely ceased to have any significant effects after controlling for maternal mental health and background, and postnatal smoking and drinking.

Based on this review of the literature, the present study was designed to examine whether prenatal and postnatal exposure to alcohol and tobacco, separately or in combination via mothers’ reports of drinking and smoking during pregnancy, had any lasting association with a wide range of children’s developmental outcomes over the first four years of primary school. Although other studies have documented the effects of maternal substance use on child health, there are several strengths of the present study:

- **First**, the prospective longitudinal study design (the BBBF Project) allowed us to determine the effects of both prenatal and postnatal substance exposure, and to assess developmental outcomes in the same children at several time-points.

- **Second**, the considerable sample size and diversity of participating families may increase the generalizability of results to other disadvantaged children in Canada.

- **Third**, we assessed effects on a wide range of child outcomes in the cognitive/academic, social/emotional, behavioural and health domains.

- **Finally**, the separate and combined effects of prenatal exposure to alcohol and tobacco were assessed.
3. Method

3.1 Data Source

This report used data from the BBBF Longitudinal Study database for analyses of the effects of prenatal and postnatal alcohol and tobacco on children's health and development outcomes during early primary school.

The BBBF Longitudinal Study is one of the most ambitious research projects on the long-term impacts of early childhood prevention programming for disadvantaged children in Canada. The diversity of the participating communities (francophone, Aboriginal, recent immigrants, and multicultural) increases the likelihood that findings will be applicable to children across Canada.

The longitudinal study began in 1993 and is following two groups of children and their families who experienced up to four years of BBBF prevention programming. One group received Better Beginning programs from birth to age 4 (the younger group), and a second group received the programs from ages 4 to 8 (the older group). Also included in the longitudinal research is a comparison group of children and their families from several demographically matched communities that did not receive BBBF funding. (See bbbf.queensu.ca/ research for a complete description of the research design and analyses.)

Data from the younger children only are included in the present study, as these children were involved in the study from 3 months of age. From 1993 to 2003, data were collected on approximately 600 children when the children were 3 months, 18 months, 33 months and 48 months, and in Grades 1 (age 6 years) and 3 (age 8 years). Data were collected by trained researchers in each community via a parent interview, direct child measures and, beginning at 48 months, from the child's teacher using a teacher report form. Over 100 outcome measures have been gathered at each data collection point, covering a wide range of child, parent/family and neighbourhood characteristics.

One of the unique features of the current study is the number of potentially confounding variables that were statistically controlled in all analyses. The measures used as covariates in all analyses were those that might bias the results due to factors other than smoking or drinking during pregnancy. By including these measures in the analyses, statistical controls were employed to remove any bias these variables may have had on the differences between groups. A complete list of the measures used as covariates in the analyses appears in Appendix 2, and includes measures of family income, maternal education, immigrant status, home language and single-parent status. Also included in this list of control variables is whether or not children resided in a BBBF or comparison community. Thus, any outcome differences resulting from Better Beginning program effects have been statistically eliminated from the following analyses.
3.2 Better Beginnings, Better Futures
Study Characteristics

The BBBF study has generated the most extensive and intensive longitudinal database involving disadvantaged children and families in Canada. The BBBF longitudinal study contains more information about early child development and parent behaviour in disadvantaged neighbourhoods than the National Longitudinal Survey of Children and Youth (NLSCY; Statistics Canada & Human Resources Development Canada, 1995), the Ontario Child Health Study (OCHS; Statistics Canada, 2004) and the Montreal Longitudinal Study (MLS; Tremblay, Mâsse, Kurtz & Vitaro, 1996). The NLSCY longitudinal samples are selected to match the general Canadian population in terms of socio-economic and other demographic variables. Hence in these longitudinal samples, there are relatively few children living in disadvantaged families. This is also true of the OCHS sample in Ontario. Further, since the OCHS and MLS began studying children longitudinally at ages 4 and 6, respectively, no data were collected in these two studies from mothers or children at or immediately following the children’s birth. Finally, neither the OCHS nor MLS collected as wide a variety of child outcome measures as the BBBF longitudinal study.

3.3 Measures of Maternal Alcohol and Tobacco Use

As part of the first parent interview, when their child was 3 months old, mothers in the BBBF study were asked a series of questions concerning, among other things, their use of alcohol and tobacco when they were pregnant with this child. These questions are similar to those used in the NLSCY and other population surveys and are presented in Table 1. The questions concerned mothers’ reports of alcohol use and cigarette smoking during their pregnancy, as well as indications of high-risk problem drinking using the four questions from the CAGE questionnaire (Ewing, 1984), and are described below.

Responses to the alcohol-use questions were categorized as “never drank,” “drank less than once per month,” “drank more than once per month.” Responses to the questions concerning cigarette smoking during pregnancy were categorized as “never smoked,” “smoked less than ½ pack per day,” “smoked more than ½ pack per day.”
### Questions in Parent Interview Concerning Maternal Alcohol Use and Smoking

**ALCOHOL**

1. Did you drink alcohol during your pregnancy?
   a. If yes, did you change the amount you drank while you were pregnant?
   b. How often did you drink alcohol during this pregnancy?
   c. When you drank alcohol during this pregnancy, how many drinks would you have, on average, each time?

**CAGE**

1. Did you ever feel that you ought to cut down on your drinking?
2. Did people annoy you by criticizing your drinking?
3. Did you ever feel bad or guilty about your drinking?
4. Did you ever have a drink first thing in the morning to steady your nerves or get rid of a hangover?

**SMOKING**

1. Did you smoke cigarettes during your pregnancy?
   a. If yes, how many cigarettes did you smoke on a typical day during this pregnancy?
   b. Did you change your smoking pattern during this pregnancy?
   c. If you stopped smoking, in which month of pregnancy did you stop?

2. Did any of the other people living in your household smoke cigarettes during your pregnancy?
   a. If yes, how many?
3.4 Sample Size

The size of the longitudinal sample at the various data collection points (i.e. child ages 33 months, 48 months, Grade 1 and Grade 3) for which prenatal alcohol and tobacco use responses were available appear in Table 2 for alcohol use and Table 3 for tobacco use. The attrition in the longitudinal sample was approximately 19% from 48 months to Grade 3. Analyses of differences between families that were maintained in the dataset compared with those that dropped out yielded no indication of bias resulting from sample attrition (see Peters et al., 2000 for a thorough discussion of these attrition analyses). More specifically, with regard to the data analyzed for the present study, there were no differences between the retained sample and those lost in terms of mothers’ reports of smoking or drinking patterns during pregnancy.

**Table 2**

<table>
<thead>
<tr>
<th>Mother’s reported drinking during pregnancy</th>
<th>Child age at time of longitudinal data collection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>33 Mos.</td>
</tr>
<tr>
<td>Never</td>
<td>414 (77.4)</td>
</tr>
<tr>
<td>&lt; once/mo.</td>
<td>89 (16.6)</td>
</tr>
<tr>
<td>&gt; once/mo.</td>
<td>32 (6.0)</td>
</tr>
<tr>
<td>Total</td>
<td>535 (100)</td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Mother’s reported smoking during pregnancy (# cig./day)</th>
<th>Child age at time of longitudinal data collection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>33 Mos.</td>
</tr>
<tr>
<td>None</td>
<td>352 (68.2)</td>
</tr>
<tr>
<td>&lt; ½ pack</td>
<td>118 (22.9)</td>
</tr>
<tr>
<td>&gt; ½ pack</td>
<td>46 (8.9)</td>
</tr>
<tr>
<td>Total</td>
<td>516 (100)</td>
</tr>
</tbody>
</table>
As shown in Tables 2 and 3, the sample size when the children were 48 months of age is approximately 500; the sample was reduced to 407 by Grade 3. Over 20% of the sample at each point in time consisted of mothers who reported some prenatal alcohol consumption; over 30% reported some prenatal tobacco exposure. Approximately 6% of these mothers reported using alcohol more than once per month during pregnancy, and 9% reported smoking more than ½ pack of cigarettes per day. These rates are higher than those reported in the Canadian Community Health Survey (see Section 2).

Approximately 99% of the children were residing with their biological mother at age 3 months, and this decreased slightly over time to 97% at age 33 months and 96% at Grade 1 and Grade 3. Due to the small number of children living with a foster parent or guardian at Grade 1 (N = 12) and Grade 3 (N = 9), it was not possible to analyze the data to see if those living with non-biological parents differed in exposure to prenatal alcohol or tobacco when compared with those living with a biological parent. Thus, the results of analyses reported here apply almost exclusively to children who were living with at least one biological parent from birth to Grade 3.

### 3.5 Sample Definition

#### 3.5.1 Tobacco Use

Due to the relatively imprecise data on the number of cigarettes smoked daily reported by the mothers, two categories of prenatal smoking were formed: those mothers that reported any smoking during pregnancy and those that reported no smoking. Thus, the smoking sample includes women who reported smoking less than a half pack per day (about two-thirds of the mothers) as well as heavier smokers.

#### 3.5.2 Alcohol Use

For prenatal alcohol consumption, several ways of categorizing the mothers’ reports of alcohol use were explored in conjunction with several of the child outcome measures. The most sensitive measure was whether the mother answered “Yes” to one or more of the four CAGE questions (see Table 1). If she did, she was considered a higher-risk drinker (MHRD) during pregnancy. If not, she was considered lower risk. The decision to use this method of identifying children who were exposed to higher versus lower risk of prenatal alcohol was based on several studies that indicated the use of scores of 1 or greater on the CAGE as being the most sensitive to problem drinking in women while scores of 2 or greater on the four CAGE questions have been found to be most sensitive to higher-risk drinking in men (Bradley, Boyd-Wickizer, Powell & Burman, 1998; Midanik, Zahnd & Klein, 1998; Moraes, Viellas & Reichenheim, 2005).
### Table 4

Sample Sizes for the Four Groups of Mothers Regarding Drinking and Smoking During Pregnancy

<table>
<thead>
<tr>
<th>Data cycles</th>
<th>Smoking during pregnancy</th>
<th>Drinking during pregnancy (CAGE)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower-risk drinker</td>
<td>Higher-risk drinker</td>
</tr>
<tr>
<td>33 Months</td>
<td>Didn’t smoke</td>
<td>302</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Smoked</td>
<td>122</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>424</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\chi^2 (1) = 10.6, \ p&lt;0.001$</td>
<td></td>
</tr>
<tr>
<td>48 Months</td>
<td>Didn’t smoke</td>
<td>298</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Smoked</td>
<td>115</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>413</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\chi^2 (1) = 12.5, \ p&lt;0.001$</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>Didn’t smoke</td>
<td>249</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Smoked</td>
<td>107</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>356</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\chi^2 (1) = 13.3, \ p&lt;0.001$</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>Didn’t smoke</td>
<td>241</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Smoked</td>
<td>97</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>338</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\chi^2 (1) = 15.6, \ p&lt;0.001$</td>
<td></td>
</tr>
</tbody>
</table>
Note that this is a behavioural definition of higher risk based on reported feelings of guilt, annoyance, sober second thought (“I ought to cut back”) and hangover avoidance by morning drinking. The guilt, annoyance and second-thought criteria are likely to have captured a substantial number of cases where the amount of drinking was moderate as well as the behaviour of very heavy drinkers. We did not try to quantify the amount of alcohol consumed in any of the analyses reported here.

There is emerging evidence that the most severe harmful effects of prenatal alcohol exposure result from mothers’ binge drinking rather than from more regular or more frequent light or moderate consumption. Although more research is needed on more subtle outcomes resulting from prenatal exposure to lower concentrations of alcohol, the higher-risk versus lower-risk dichotomy of mothers’ prenatal alcohol consumption based on a CAGE score of 1 or more was adopted for analyses of children’s prenatal exposure to alcohol in this study.

3.5.3 Prevalance of Alcohol and Tobacco Use During Pregnancy

This strategy divided mothers into four groups regarding alcohol use and smoking during pregnancy: 1) higher-risk drinking, smoking; 2) higher-risk drinking, non-smoking; 3) lower-risk drinking, smoking; 4) lower-risk drinking, non-smoking (see Table 4 for sample sizes).

The chi-square statistical test results reported at each age reflect a highly statistically positive relationship between mothers’ reports of prenatal smoking and their reports of high-risk drinking.

We decided that the BBBF longitudinal data set contained enough detailed information on mothers’ alcohol and tobacco use during pregnancy to warrant further analyses concerning relationships with children’s development, school readiness and functioning during early primary school. The sample sizes were considered to be adequate to allow analyses of the independent and combined association between prenatal exposure to alcohol and to tobacco, with a wide range of measures of child development.

3.6 Measures of Child Development

The BBBF dataset has measures of five major domains of children’s development.

1. Children’s general development
2. Cognitive development/ academic performance,
3. Social/emotional functioning
4. Behaviour problems
5. Child health

These domains correspond closely with the five domains of school readiness currently employed in Canada (Janus & Offord, 2000). A total of 79 child outcome measures were selected for preliminary analysis. Most of these measures were collected when the children were 48 months, 6 years (Grade 1) and 8 years (Grade 3) of age. Three of the measures had been collected when the children were 33 months old. The specific child outcome measures selected for analysis are listed in Appendix 1 for each of the five domains of child development.
4. Data Analysis

4.1 Data Analysis Part 1: ANCOVA

Analyses of the 79 child outcome measures were carried out using Analyses of Covariance (ANCOVA) with the mother’s drinking alcohol and smoking during pregnancy as the two independent variables. The general idea of ANCOVA is to use statistical methods to create a level playing field for the comparisons of groups. The measures used as covariates in the ANCOVA analyses were those that might bias the results due to factors other than smoking or drinking during pregnancy. By including these measures in the analyses, statistical controls were used to remove any bias these variables may have had on the differences between groups. A complete list of the measures used as covariates in the analyses appears in Appendix 2, and includes measures of family income, maternal education, immigrant status, home language and single-parent status.

With the four prenatal smoking and drinking groups statistically equated on the covariate variables, we could then compare the average results for different groups with increased confidence. We compared the averages in a statistical manner so that we were less tempted to seize on a false result that favours our hypotheses.

4.1.1 Statistical Significance

It is standard practice to report the results of statistical analyses in terms of significance levels or p values. In the current analyses, the significance level (p value) is the probability that the difference between groups on any given measure is due to chance factors alone. If the p value is low (i.e. .01 or less), we can conclude that differences between groups are likely to be due to differences in whether or not mothers drank or smoked during pregnancy rather than being due to chance. If the p value is .01 or less, we conclude that the group differences are statistically significant. Statistically significant results allow us to say something similar to the phrase used in consumer polls; we will be right at least 99 times out of 100 whenever we say that the averages of two groups are in fact different, and not due to chance. We chose to use a conservative p value of .01 because of the large number of tests we were reporting.

4.1.2 Effect Size

The effect size reflects how large average differences are across different variables in a standardized manner. One of the problems with using many different measures is that the numbers used mean different things from one measure to another. A difference of 10 points means one thing in a depression score and another in an IQ score. In an effort to produce numbers that mean the same thing from measure to measure, we calculated a statistic called an effect size (more specifically a d statistic). When we compare two groups of children, the d statistic allows us to express the difference between the two groups in units determined by the variability of the children within their groups. This gives a common metric across measures and effectively allows us to compare “apples to oranges.”
In social and health science research, it is convention to consider effect size (E.S.) indices as small if the value is between .2 and .5; medium if between .5 and .8; and large if the E.S. is .8 or greater. We report effect sizes for our all analyses where the data are available (including statistically significant and non-significant results). Note that for non-significant effect sizes, we have no confidence that the observed value of the effect size is dependably greater than 0.0.

4.2 Data Analysis Part 2: Structural Equation Modelling

For the Structural Equation Modelling (SEM) analysis of the relationship between measures of maternal tobacco and alcohol consumption and later internalizing and externalizing behaviours, we limited the analysis to the four measures of smoking and drinking behaviour (and two arithmetic products of those measures), four measures of externalizing behaviours and two measures of internalizing behaviours collected from the teachers of the children and the same from the parents of the children.

The earliest measures were the tobacco use and alcohol use measures collected from mothers when the children were 3 months old. These are the same measures described in Table 1, and were coded dichotomously (i.e. higher-risk drinking versus no high-risk drinking; any smoking during pregnancy versus no smoking). The product of the two measures was used as a third variable, sensitive to an interaction between tobacco and alcohol use. Note that the product gave the non-drinkers and non-smokers the same value as the non-drinking smokers and the non-smoking drinkers. Thus, these “one substance only” cases were included in the SEM analysis while they were omitted from the ANCOVA analyses described above.

When the children were 33 months old, we also collected data on maternal alcohol use and smoking in the home (as an indication of exposure to second-hand smoke). These were coded dichotomously and the product computed. This gave us a total of six measures of smoking and drinking behaviour, three collected at each of two times.

When the child was in Grade 3, we collected a large array of measures of child behaviour and social and emotional functioning, as described above. From that list of measures, we chose six parent report measures and six teacher measures that would allow us to estimate externalizing behaviour and internalizing behaviour. The measures are listed below.

4.1.3 Analysis Process

Each of the child outcome measures was analyzed three ways. First, outcomes for children of the smoking mothers were compared with children of the non-smoking mothers. This allowed for a comparison of children exposed to any prenatal tobacco to those exposed to none. A second analysis compared outcomes for children of the high-risk drinking mothers to those of low-risk drinking mothers. A third analysis compared children of mothers who were both high-risk drinkers and smokers to those who were low-risk drinkers and non-smokers. This comparison allowed for an assessment of the outcomes of children exposed to both prenatal tobacco and high levels of alcohol.
### 4.2.1 Parent Measures

*Internalizing measures (distress and emotion)*
- OCHS parent-rated depression scale
- NLSCY parent-rated emotional disorder scale

*Externalizing measures (misbehaviour and problem behaviour)*
- OCHS parent-rated oppositional defiant scale
- NLSCY parent-rated indirect aggression scale
- NLSCY parent-rated hyperactive scale
- NLSCY parent-rated physical aggression scale

### 4.2.2 Teacher Measures

*Internalizing measures (distress and emotion)*
- OCHS teacher-rated passive victimization scale
- NLSCY teacher-rated emotional disorder scale

*Externalizing measures (misbehaviour and problem behaviour)*
- NLSCY teacher-rated delinquency scale
- NLSCY teacher-rated indirect aggression scale
- NLSCY teacher-rated hyperactivity scale
- NLSCY teacher-rated physical aggression scale

### 4.2.3 Procedure

We controlled for the same covariates described above by computing the covariate adjusted residuals for our Grade 3 parent and teacher variables (12 measures).

The data were analyzed using AMOS 17.0 (SPSS; Levesque 2007). Although AMOS does not have an option for selecting list-wise/pair-wise deletion, it can handle missing cases using a method called “Full Information Maximum Likelihood” (FIML, also known as “Raw Maximum Likelihood”), which is the technique that we used to deal with missing cases. This technique leads to indefinite sample sizes because while 502 people contributed data, only 177 have complete data for all 18 variables. Classical list-wise deletion would have limited the analysis to the information provided by the 177 subjects with complete data. The FIML procedure uses all the information available from the 502 subjects while assessing for bias imposed by the procedure. Given that the missing data were randomly missing, this technique is more efficient.

The SEM analysis was broken into segments to simplify the process. One segment modeled the relationships among the alcohol and tobacco measures, another tackled the internalizing and externalizing measures.
5. Results

5.1 Results of the ANCOVA

ANCOVA analyses were carried out on a total of 79 child outcome measures collected as part of the BBBF longitudinal study when children were 33 months, 48 months, 6 years (Grade 1) and 8 years (Grade 3) of age. Each measure was independently analyzed using Analysis of Covariance (ANCOVA) procedures. For each measure, children exposed to tobacco during pregnancy were compared with those not exposed, yielding the Prenatal Exposure to Tobacco, or PET effect. Also, children whose mothers were considered higher risk for problem drinking during pregnancy based on a CAGE score of 1 or higher were compared with children whose mothers were considered lower risk, the Maternal Higher-Risk Drinker, or MHRD effect. Finally, for each measure, the PET and MHRD group was compared with the non-PET and non-MHRD group. This comparison was designed to determine the effects of the combination of prenatal exposure to tobacco plus maternal higher-risk drinking during pregnancy. For all analyses, the set of family socio-economic, cultural and demographic variables listed in Appendix 2 were employed as covariates to eliminate confounding effects of these variables associated with maternal prenatal tobacco use or higher-risk drinking. Appendix 1 presents a summary of the results of the three statistical comparisons of all 79 child outcome measures.

Since these three hypotheses are all directional in nature, one-tailed statistical tests of significance were used for all analyses. Also, the results in Appendix 1 are presented in terms of whether each analysis yielded a difference in means in the hypothesized direction (i.e. poorer performance represented by a negative sign (–), or a difference in means in the opposite direction from that hypothesized, represented by a plus sign (+)).

In this section, all statistically significant results are presented and described (the non-significant (NS) results are reported in Appendix 1). For each statistically significant effect ($p < .01$), the effect size (E.S.) is presented where the E.S. reflects how large the mean difference is in standard deviation units.

- In social and health science research, an E.S. of .2 to .5 is considered small, .5 to .8 moderate, and >.8 is considered large (Cohen, 1977).

The results are presented separately according to the domain of child functioning reflected by the measures. Group means, standard errors and sample sizes for the analyses of all variables are presented in Appendix 3.
### 5.1.1 Child General Development

As summarized in Table 5, statistically significant results occurred for all three measures of children’s general development: the Developmental Inventory for Screening Children (DISC) Overall score at 33 and 48 months of age and the ABC School Readiness. **Children exposed to tobacco and higher-risk alcohol use by their mothers during pregnancy showed significantly poorer outcomes on the three measures of general development compared with the group of children who were not exposed to either tobacco or high-risk maternal drinking during pregnancy** (i.e. the PET and MHRD comparison).

![Table 5](image)

The effect sizes for these group differences ranged from –.50 to –.65, differences that are considered to be moderate in size.

There were no statistically significant effects of exposure to tobacco alone, or exposure to higher-risk maternal alcohol use alone.

---

**Table 5**

<table>
<thead>
<tr>
<th>Measure and Age of Child</th>
<th>Prenatal Exposure to Tobacco (PET)</th>
<th>Mother Higher risk Drinker (MHRD)</th>
<th>PET and MHRD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At 33 months of age (1 measure)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developmental Inventory for Screening Children (DISC) Overall Development Quotient (E= measure collected directly from the child by a trained researcher)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>-.57</td>
</tr>
<tr>
<td><strong>At 48 months (2 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DISC overall Developmental Quotient (E)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>-.50</td>
</tr>
<tr>
<td>ABC School Readiness (T=Teacher rating)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>-.65</td>
</tr>
<tr>
<td><strong>Summary (3 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># significant / # of tests</td>
<td>0/3</td>
<td>0/3</td>
<td>3/3</td>
</tr>
<tr>
<td>% significant</td>
<td>0%</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

E = measure collected directly from trained researcher  
T = measure collected from teacher
5.1.2 Children’s Cognitive Development and Academic Performance Measures

There were a total of 23 measures analyzed in the domain of children’s cognitive development and academic performance, and the results of these analyses are summarized in Table 6. Of the 23 measures, 7 showed statistically significant differences, with the children exposed to both tobacco and mother’s higher-risk drinking during pregnancy showing poorer performance when compared with the group that was exposed to neither. Six of these group differences yielded effect sizes in the moderate range (.52–.69), but the measure of teacher ratings of the child’s school preparedness in Grade 3 yielded a much larger difference, with an effect size of 1.03. (Note: E = directly

Table 6

<table>
<thead>
<tr>
<th>Measure and Age of Child</th>
<th>Prenatal Exposure to Tobacco (PET)</th>
<th>Mother Higher risk Drinker (MHRD)</th>
<th>PET and MHRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 months of age (1 measure)</td>
<td>None Significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 months (3 measures)</td>
<td>DISC Auditory of Memory Scale (E) N.S.</td>
<td>–.44</td>
<td>–.63</td>
</tr>
<tr>
<td>Grade 1 (8 measures)</td>
<td>None significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 (11 measures)</td>
<td>School preparedness (T) N.S.</td>
<td>–.69</td>
<td>–1.03</td>
</tr>
<tr>
<td></td>
<td>Attitudes toward academics (T) N.S.</td>
<td>–.53</td>
<td>–.69</td>
</tr>
<tr>
<td></td>
<td>Academic functioning (T) N.S.</td>
<td>–.58</td>
<td>–.65</td>
</tr>
<tr>
<td></td>
<td>Adaptive functioning (T) N.S.</td>
<td>N.S.</td>
<td>–.62</td>
</tr>
<tr>
<td></td>
<td>Suspended from school (P = Parent rating) N.S.</td>
<td>N.S.</td>
<td>–.56</td>
</tr>
<tr>
<td></td>
<td>Special ed. services (T) N.S.</td>
<td>N.S.</td>
<td>–.64</td>
</tr>
<tr>
<td>Summary (23 Measures)</td>
<td># significant/# of tests</td>
<td>0/23</td>
<td>4/23</td>
</tr>
<tr>
<td></td>
<td>% significant</td>
<td>0%</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>T = teacher-rated measure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P = parent-rated measure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
from trained researcher, T = teacher, and P = parent indicate the source of each measure). Of the 7 significant effects, 6 were on measures collected when the children were in Grade 3, and 5 of these 6 were based on ratings by the child’s teacher.

There were also 4 significant negative effects of children exposed to higher-risk mother’s drinking during pregnancy. There were no differences on any of the 23 measures associated with exposure to tobacco during pregnancy.

**Table 7**

<table>
<thead>
<tr>
<th>Measure and Age of Child</th>
<th>Prenatal Exposure to Tobacco (PET)</th>
<th>Mother Higher risk Drinker (MHRD)</th>
<th>PET and MHRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 months (1 measure)</td>
<td>None significant</td>
<td>None significant</td>
<td>None significant</td>
</tr>
<tr>
<td>48 months (6 measures)</td>
<td>None significant</td>
<td>None significant</td>
<td>None significant</td>
</tr>
<tr>
<td>Grade 1 (8 measures)</td>
<td>None significant</td>
<td>None significant</td>
<td>None significant</td>
</tr>
<tr>
<td>Grade 3 (N=8)</td>
<td>Emotional disorder (T)</td>
<td>N.S.</td>
<td>-.65</td>
</tr>
<tr>
<td></td>
<td>Conflict management (T)</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td></td>
<td>Emotional disorder (T)</td>
<td></td>
<td>-.80</td>
</tr>
<tr>
<td></td>
<td>Conflict management (T)</td>
<td></td>
<td>-.60</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td># significant/# of tests</td>
<td>0/23</td>
<td>1/23</td>
</tr>
<tr>
<td></td>
<td>% significant</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>T = teacher-rated measure</td>
<td></td>
<td>9%</td>
</tr>
</tbody>
</table>
5.1.3 Children’s Social/Emotional Functioning Measures

A total of 23 measures of various aspects of children’s social and emotional functioning were analyzed and the results are summarized in Table 7. Only 2 measures yielded statistically significant differences – teachers’ ratings of children’s emotional problems and their ability to manage conflict with peers at Grade 3. Children exposed to both tobacco and higher-risk maternal drinking during pregnancy showed higher levels of emotional problems and poorer conflict management, as rated by their teachers, than those children exposed to neither. Also, children exposed to higher-risk maternal drinking showed higher levels of emotional problems in Grade 3 than children not exposed to higher-risk maternal drinking. Again, there was no indication of compromised social or emotional functioning associated with children being exposed to tobacco during pregnancy.

### Table 8

<table>
<thead>
<tr>
<th>Measure and Age of Child</th>
<th>Prenatal Exposure to Tobacco (PET)</th>
<th>Mother Higher risk Drinker (MHRD)</th>
<th>PET and MHRD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>48 months (3 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grade 1 (3 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child exposed to second-hand smoke (P)</td>
<td>−.79</td>
<td>N.S.</td>
<td>−.83</td>
</tr>
<tr>
<td><strong>Grade 3 (3 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child exposed to second-hand smoke (P)</td>
<td>−.64</td>
<td>N.S.</td>
<td>−.49</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># significant/# of tests</td>
<td>2/9</td>
<td>0/9</td>
<td>2/9</td>
</tr>
<tr>
<td>% significant</td>
<td>22%</td>
<td>0%</td>
<td>22%</td>
</tr>
</tbody>
</table>

P = parent-rated measure
### Table 9

**Child Behaviour Problems: Effect Sizes for Statistically Significant (p < .01, 1-tailed) Measures**

<table>
<thead>
<tr>
<th>Measure and Age of Child</th>
<th>Prenatal Exposure to Tobacco (PET)</th>
<th>Mother Higher risk Drinker (MHRD)</th>
<th>PET and MHRD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>33 months (1 measure)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>48 months (5 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disruptive behaviour (T)</td>
<td>N.S.</td>
<td>–.52</td>
<td>–.83</td>
</tr>
<tr>
<td>Hyperactivity (T)</td>
<td>N.S.</td>
<td>–.52</td>
<td>–.88</td>
</tr>
<tr>
<td>Indirect aggression (T)</td>
<td>N.S.</td>
<td>–.61</td>
<td>–.84</td>
</tr>
<tr>
<td>Physical aggression (T)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>–.85</td>
</tr>
<tr>
<td><strong>Grade 1 (8 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delinquency (T)</td>
<td>N.S.</td>
<td>–.69</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Grade 3 (8 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical aggression (P)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>–.59</td>
</tr>
<tr>
<td>Hyperactivity (T)</td>
<td>N.S.</td>
<td>–.56</td>
<td>–.77</td>
</tr>
<tr>
<td>Indirect aggression (T)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>–.86</td>
</tr>
<tr>
<td>Physical aggression (T)</td>
<td>N.S.</td>
<td>–.49</td>
<td>–.76</td>
</tr>
<tr>
<td>Delinquency (T)</td>
<td>N.S.</td>
<td>–.66</td>
<td>–.98</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># significant/# of tests</td>
<td>0/22</td>
<td>6/22</td>
<td>10/22</td>
</tr>
<tr>
<td>% significant</td>
<td>0%</td>
<td>27%</td>
<td>45%</td>
</tr>
</tbody>
</table>

T = teacher-rated measure  
P = parent-rated measure
5.1.4 Children’s Health Measures

Of the 9 measures reflecting children’s health at various ages, only the measure of children being exposed to second-hand smoke yielded statistically significant effects in Grades 1 and 3. This is not, strictly speaking, a child outcome measure; instead, it reflects the fact that children whose mothers reported smoking during pregnancy as well as those who reported smoking and higher-risk drinking during pregnancy also indicated that their children were exposed to more second-hand smoke when in Grades 1 and again in Grade 3. No other measure of child health showed any indication of negative effects associated with either smoking or higher-risk drinking during pregnancy.

5.1.5 Children’s Behaviour Problems Measures

There were 22 measures of children’s behaviour problems. As summarized in Table 9, children who were exposed to both tobacco and higher-risk maternal drinking during pregnancy showed significantly higher levels of several types of behaviour problems than children exposed to neither. Of 22 measures analyzed, 10 were statistically significant, and 9 of the 10 significant effects were on ratings by the child’s teacher, primarily at 4 years of age and again in Grade 3. Further, most of these differences were quite large, yielding effect sizes near or above .80.

Six of the 22 behaviour problem measures were also significantly higher for children who were exposed to higher-risk maternal drinking during pregnancy compared with children not exposed. All 6 of these significant effects were on ratings by the child’s teacher, 3 when the children were 4 years old and 3 when they were in Grade 3. (Note: This is covered in some detail in the discussion section.) Again, there was no indication of an association between children’s prenatal exposure to tobacco and later ratings of behaviour problems.
5.1.6 Summary of Significant Child Outcomes

In this final section of results, we attempt to summarize the main findings of the analyses just described. The first summary is presented in Table 10. Here we show the number and percentages of outcome measures in each child domain that yielded statistically significant results.

The first column presents the results of comparisons between children who were exposed to some tobacco prenatally and those exposed to no tobacco, the PET effect. Out of the 79 measures analyzed, only 2 were statistically significant. Those were the measures of exposure to second-hand smoke at Grades 1 and 3, a finding that indicates the children of mothers who smoked during pregnancy were exposed to more second-hand smoke at ages 6 and 8 than children of mothers who did not smoke during pregnancy. There were no other significant outcomes in any of the other 79 measures associated with smoking versus no smoking during pregnancy. As discussed previously, although exposure to second-hand smoke is

### Table 10

#### Summary of Statistically Significant (p < .01, 1-tailed) Child Outcome Effects by Domain

<table>
<thead>
<tr>
<th>Child Domain Measured</th>
<th>Prenatal Exposure to Tobacco (PET)</th>
<th>Mother Higher risk Drinker (MHRD)</th>
<th>PET and MHRD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child Development (3 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># significant/# of tests</td>
<td>0/3</td>
<td>0/3</td>
<td>3/3</td>
</tr>
<tr>
<td>% significant</td>
<td>0%</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>Average of significant effects</td>
<td></td>
<td></td>
<td>−.57</td>
</tr>
<tr>
<td>Average of all effect sizes</td>
<td>−.29</td>
<td>−.28</td>
<td>−.57</td>
</tr>
<tr>
<td><strong>Cognitive Development/Academic Performance (23 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># significant/# of tests</td>
<td>0/23</td>
<td>4/23</td>
<td>7/23</td>
</tr>
<tr>
<td>% significant</td>
<td>0%</td>
<td>17%</td>
<td>30%</td>
</tr>
<tr>
<td>Average of significant effects</td>
<td></td>
<td></td>
<td>−.56</td>
</tr>
<tr>
<td>Average of all effect sizes</td>
<td>−.18</td>
<td>−.29</td>
<td>−.69</td>
</tr>
<tr>
<td><strong>Social/Emotional Functioning (22 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># significant/# of tests</td>
<td>0/22</td>
<td>1/22</td>
<td>2/22</td>
</tr>
<tr>
<td>% significant</td>
<td>0%</td>
<td>4%</td>
<td>9%</td>
</tr>
<tr>
<td>Average of significant effects</td>
<td></td>
<td></td>
<td>−.65</td>
</tr>
<tr>
<td>Average of all effect sizes</td>
<td>−.13</td>
<td>−.18</td>
<td>−.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
unhealthy, it is not truly a child health outcome such as asthma or physical illness, so this effect needs to be viewed with some caution.

Column 2 summarizes the results of comparisons between children whose mothers engaged in higher-risk drinking during pregnancy versus children of mothers who were not higher-risk drinkers, the MHRD effect. Eleven of the 79 analyses (14%) were statistically significant. Six of these 11 effects involved high levels of behaviour problems for children of higher-risk drinking mothers, and 4 involved poorer cognitive development for this group. Thus, the negative effects associated with children of mothers who engaged in higher-risk drinking during pregnancy are manifested primarily in poorer cognitive and academic functioning and also greater manifestation of behaviour problems such as aggression and hyperactivity.

Column 3 of Table 10 (PET and MHRD) summarizes the results of the comparison between the children who were exposed to both maternal smoking and higher-risk drinking

<table>
<thead>
<tr>
<th>Child Domain Measured</th>
<th>Prenatal Exposure to Tobacco (PET)</th>
<th>Mother Higher risk Drinker (MHRD)</th>
<th>PET and MHRD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># significant/# of tests</td>
<td>% significant</td>
<td></td>
</tr>
<tr>
<td>Child Health (9 measures)</td>
<td>2/9</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>% significant</td>
<td>0%</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>Average of significant effects</td>
<td>-.72</td>
<td>-.66</td>
</tr>
<tr>
<td></td>
<td>Average of all effect sizes</td>
<td>-.23</td>
<td>-.07</td>
</tr>
<tr>
<td>Behaviour Problems (22 measures)</td>
<td># significant/# of tests</td>
<td>% significant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0/22</td>
<td>0%</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td>% significant</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Average of significant effects</td>
<td>-.56</td>
<td>-.81</td>
</tr>
<tr>
<td></td>
<td>Average of all effect sizes</td>
<td>-.25</td>
<td>-.28</td>
</tr>
<tr>
<td>Summary (Total of 79 measures)</td>
<td># significant/# of tests</td>
<td>% significant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/79</td>
<td>2%</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>% significant</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Average of significant effects</td>
<td>-.72</td>
<td>-.59</td>
</tr>
<tr>
<td></td>
<td>Average of all effect sizes</td>
<td>-.20</td>
<td>-.23</td>
</tr>
</tbody>
</table>
## Table 11

### Summary of Statistically Significant (p < .01, 1-tailed) Child Outcome Effects by Child’s Age

<table>
<thead>
<tr>
<th>Age of Child</th>
<th>Prenatal Exposure to Tobacco (PET)</th>
<th>Mother Higher risk Drinker (MHRD)</th>
<th>PET and MHRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 Months (3 measures)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># significant/# of tests</td>
<td>0/3</td>
<td>0/3</td>
<td>1/3</td>
</tr>
<tr>
<td>% significant</td>
<td>0%</td>
<td>0%</td>
<td>33%</td>
</tr>
<tr>
<td>Mean significant effect size</td>
<td></td>
<td></td>
<td>–.57</td>
</tr>
<tr>
<td>48 Months (19 measures)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># significant/# of tests</td>
<td>0/19</td>
<td>4/19</td>
<td>7/19</td>
</tr>
<tr>
<td>% significant</td>
<td>0%</td>
<td>21%</td>
<td>37%</td>
</tr>
<tr>
<td>Mean significant effect size</td>
<td></td>
<td></td>
<td>–.52</td>
</tr>
<tr>
<td>6 years (Grade 1) (27 measures)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># significant/# of tests</td>
<td>1/27</td>
<td>0/27</td>
<td>2/27</td>
</tr>
<tr>
<td>% significant</td>
<td>4%</td>
<td>0%</td>
<td>9%</td>
</tr>
<tr>
<td>Mean significant effect size</td>
<td>–.79</td>
<td></td>
<td>–.76</td>
</tr>
<tr>
<td>8 years (Grade 3) (30 measures)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># significant/# of tests</td>
<td>1/30</td>
<td>7/30</td>
<td>14/30</td>
</tr>
<tr>
<td>% significant</td>
<td>3%</td>
<td>20%</td>
<td>47%</td>
</tr>
<tr>
<td>Mean significant effect size</td>
<td>–.64</td>
<td>–.59</td>
<td>–.72</td>
</tr>
<tr>
<td>Summary (Total of 79 measures)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># significant/# of tests</td>
<td>2/79</td>
<td>11/79</td>
<td>24/79</td>
</tr>
<tr>
<td>% significant</td>
<td>2%</td>
<td>14%</td>
<td>30%</td>
</tr>
<tr>
<td>Mean significant effect size</td>
<td>–.72</td>
<td>–.59</td>
<td>–.72</td>
</tr>
</tbody>
</table>
during pregnancy versus children who were not exposed to either smoking or higher-risk drinking. Here 24 of 79 or 30% of the statistical comparisons were significant and, as for the MHRD comparisons, the differences were most pronounced in poorer cognitive and academic functioning as well as higher levels of behaviour problems.

In Table 11, the results of the analyses are reorganized according to the age of the child when the statistically significant effects occurred. The picture that emerges from the results in Table 11 is clear. The poorer performance of children exposed to higher-risk maternal drinking during pregnancy, either alone or in combination with prenatal tobacco exposure, occurred predominantly on measures collected when children were 4 years of age or 8 years of age, with very few effects noted at age 6 (Grade 1).

The final way in which we summarized the significant findings is in terms of the three data collection sources. Some measures were collected directly from the child by trained researchers in each neighbourhood. These measures included standardized cognitive and language lists such as the Peabody Picture Vocabulary Test (PPVT); the Wechsler Block Design Test; the Developmental Inventory for Screening Children (DISC), and height, weight, EQAO reading, math and writing scores from school records at Grade 3.

Many of the measures were collected from parents through a lengthy in-home interview.

- Of the 79 measures analyzed for this report, 11 were collected by the local site researchers, directly or indirectly from the child.

- Of the 79 child outcome measures, 31 were based on parents’ reports, while 37 were provided by the child’s teachers via a teacher report form that they completed on each child in the longitudinal research sample when the children were in junior kindergarten (age 4), Grade 1 (age 6) and Grade 3 (age 8) (See Discussion section.)
### Table 12

**Summary of Statistically Significant (p < .01, 1-tailed) Child Outcome Effects by Data Collection Source**

<table>
<thead>
<tr>
<th>Child Domain Measured</th>
<th>Prenatal Exposure to Tobacco (PET)</th>
<th>Mother Higher risk Drinker (MHRD)</th>
<th>PET and MHRD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child Development (3 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Researcher collected (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent rated (0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teacher rated (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cognitive Development/Academic Performance (23 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Researcher collected (7)</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Parent rated (4)</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Teacher rated (12)</td>
<td></td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td><strong>Social/Emotional Functioning (22 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Researcher collected (0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent rated (10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teacher rated (12)</td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Child Health (9 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Researcher collected (2)</td>
<td>2</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Parent rated (7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teacher rated (0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Behaviour Problems (22 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Researcher collected (0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent rated (10)</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Teacher rated (12)</td>
<td>6</td>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>
## Table 12 (cont’d)

### Summary of Statistically Significant (p < .01, 1-tailed) Child Outcome Effects by Data Collection Source

<table>
<thead>
<tr>
<th>Child Domain Measured</th>
<th>Prenatal Exposure to Tobacco (PET)</th>
<th>Mother Higher risk Drinker (MHRD)</th>
<th>PET and MHRD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary (Total of 79 measures)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Researcher collected (11 measures)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># significant/# of tests</td>
<td></td>
<td>1/11</td>
<td>3/11</td>
</tr>
<tr>
<td>% significant</td>
<td></td>
<td>9%</td>
<td>27%</td>
</tr>
<tr>
<td>Mean significant effect size</td>
<td></td>
<td>-.44</td>
<td>-.57</td>
</tr>
<tr>
<td>Parent rated (31 measures)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># significant/# of tests</td>
<td></td>
<td>2/31</td>
<td>0/31</td>
</tr>
<tr>
<td>% significant</td>
<td></td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Mean significant effect size</td>
<td></td>
<td>-.72</td>
<td></td>
</tr>
<tr>
<td>Teacher rated (37 measures)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># significant/# of tests</td>
<td></td>
<td>0/37</td>
<td>10/37</td>
</tr>
<tr>
<td>% significant</td>
<td></td>
<td>0%</td>
<td>27%</td>
</tr>
<tr>
<td>Mean significant effect size</td>
<td></td>
<td>-.58</td>
<td></td>
</tr>
</tbody>
</table>

The significant outcome results for each of these three data sources are presented in Table 12 separately for each of the five child domains. As in previous summaries, Table 12 highlights the fact that most significant outcomes occurred on measures in the two domains of Cognitive/Academic Performance and Behaviour Problems associated with mother’s higher-risk drinking during pregnancy either alone (MHRD) or also including smoking during pregnancy (MHRD and PET).

Of the 11 statistically significant effects in the domains of cognitive/academic performance, 8 resulted from measures provided by teachers. In the domain for behaviour problems, 15 of the 16 significant effects were based on ratings provided by teachers. Overall, in all five domains of measures, there were 37 significant outcomes and 27 of these were based on teacher-provided data.
5.1.7 Summary of Major Findings of ANCOVA Analysis

The major findings from the ANCOVA analysis can be summarized as follows:

- Higher-risk drinking, as defined by scores on the CAGE screening test for alcoholism, was associated with poorer child cognitive/academic performance and more child behaviour problems during early primary school.
- The negative effects of problem drinking during pregnancy on children’s academic performance and behaviour problems were exacerbated if the mothers also reported smoking cigarettes during the pregnancy.
- There was little indication of any long-term negative effects on children’s behaviour associated with their mother’s smoking during pregnancy. The only negative effects associated with smoking during pregnancy were greater child exposure to second-hand smoke reported by parents when the children were 6 and 8 years of age. Although this is an undesirable outcome for children, there was no indication of poorer general health, more asthma or reduced growth during primary school in children exposed to tobacco prenatally.
- There were a total of 37 statistically significant outcome effects, all of which indicated a negative relationship between prenatal higher-risk drinking alone or in conjunction with smoking. Of these 37 effects, 33 or 90% occurred on measures collected at junior kindergarten (age 4) or Grade 3 (age 8). There were virtually no negative effects noted on measures collected when the children were in Grade 1 (age 6). This is especially true if the measures of second-hand smoke are discounted.
- As noted above, there were 33 significant effects indicating a negative association between prenatal higher-risk drinking and behaviour problems in junior kindergarten and Grade 3. Of these 33 effects, 27 or 82% were based on teacher ratings of the children’s academic performance and behaviour.

5.2 Results of the Structural Equation Modelling

5.2.1 Drinking and Smoking

Although the modelling of the smoking and drinking measures was an exploratory analysis, we were able to use both order effects and structural relationships to simplify the model (we assumed that measures taken at 33 months did not have a causal effect on measures taken at 3 months). We placed the measures of smoking and drinking behaviour prior to the product of those two variables. All variables in this model were manifest variables (i.e. they were measured directly and included the six drinking and smoking variables listed in Figure 1). We chose to limit paths to those between measures of the same behaviour at different times and to measures of different behaviour at the same time. Figure 1 (Drinking and Smoking Structural Equation Model) shows the results of the modelling. With a Root Mean Square Error of Approximation (RMSEA) of .062 and Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI) of .988 and .965, respectively, the model is a good enough fit to the data.
Children’s Prenatal & Postnatal Exposure to Alcohol and Tobacco

Figure 1

**Drinking and Smoking Structural Equation Model**

**Fit Index:**
- CFI = .988
- TLI = .965
- RMSEA = .062

- **Drink1** = higher-risk drinking during pregnancy
- **Drink2** = higher-risk drinking at 33 months
- **Smoke1** = mother’s smoking during pregnancy
- **Smoke2** = child exposed to second-hand smoking at 33 months
- **INT1** = Smoke1 + Drink1
- **INT2** = Smoke2 + Drink2
- **err** = error component. These reflect the portion of the measure that is not measuring the construct of interest, but rather some unknown or random phenomenon – hence error or disturbance.
5.2.2 Parent and Teacher Ratings of Internalizing and Externalizing Behaviour

This analysis is a confirmatory factor analysis of the six measures rated by teachers and the six measures rated by parents. The internalizing/externalizing split is a well-established relationship closely associated with, but not limited to, the Achenbach measures (e.g. Achenbach & Rescoria, 2001). Our preliminary attempts at fitting models that incorporated both teacher and parent data produced either trivial or ill-fit models, so we split the models into a teacher model and a parent model, as presented below in Figure 2 (Parent Confirmatory Factor Analysis) and Figure 3 (Teacher Confirmatory Factor Analysis).

Both models have adequate, but not great goodness of fit (Teacher RMSEA = .091, CFI = .944, TLI = .852; Parent RMSEA = .083, CFI = .963, TLI = .904) with the parent fit appearing to be somewhat better than the teacher fit.

**Figure 2**

Parent Confirmatory Factor Analysis

**Fit Index:**
- CFI = .963
- TLI = .904
- RMSEA = .083

![Diagram](Diagram.png)

**Formulae:**
- \( P_{\text{internal}} = \) parent ratings of internalizing behaviour problems
- \( pemoG3r = \) parent ratings of emotional disorder at Grade 3
- \( pdpG3r = \) parent ratings of depression scale at Grade 3
- \( pindG3r = \) parent ratings of indirect aggression at Grade 3
- \( podG3r = \) parent ratings of oppositional defiant behaviour at Grade 3
- \( pphyG3r = \) parent ratings of physical aggression at Grade 3
- \( phypG3r = \) parent ratings of hyperactivity at Grade 3
- err = error component. These reflect the portion of the measure that is not measuring the construct of interest, but rather some unknown or random phenomenon – hence error or disturbance.
Next, we linked the smoking/drinking model with the teacher model and then with the parent model to estimate paths from smoking and drinking measures to latent traits of externalizing and internalizing behaviors (the latent traits are the factors – teacher internalizing, teacher externalizing, parent internalizing and parent externalizing. They are latent in that they are not measured directly; rather, they are inferred from the behavior of other variables). The unreduced model had 12 paths from the six predictor manifest variables to the two latent trait outcome variables. Using a reverse stepwise technique, we deleted the smallest path with p value greater than .2 until every remaining path on the diagram from the tobacco/alcohol variables to the internalizing/externalizing variables had a p value of .2 or smaller. These results are presented in Figure 4 (Parent-Reduced Model) and Figure 5 (Teacher-Reduced Model).

**Figure 3**

**Teacher Confirmatory Factor Analysis**

**Fit Index:**

CFI = .944  
TLI = .852  
RMSEA = .091

T_internal = teacher ratings of internalizing behaviour problems  
temoG3r = teacher ratings of emotional disorder at Grade 3  
tpvG3r = teacher ratings of passive victimization scale at Grade 3  
T_external = teacher ratings of externalizing behaviour problems  
tphyG3r = teacher ratings of physical aggression at Grade 3  
thypG3r = teacher ratings of hyperactivity at Grade 3  
tindG3r = teacher ratings of indirect aggression at Grade 3  
tdelG3r = teacher ratings of delinquency at Grade 3  
err = error component. These reflect the portion of the measure that is not measuring the construct of interest, but rather some unknown or random phenomenon – hence error or disturbance.
Figure 4

Parent-Reduced Model

Fit Index:
CFI = .964
TLI = .942
RMSEA = .054

Drink1 = higher-risk drinking during pregnancy
Drink2 = higher-risk drinking at 33 months
Smoke1 = mother’s smoking during pregnancy
Smoke2 = child exposed to second-hand smoking at 33 months
Int1 = Smoke1 + Drink1
Int2 = Smoke2 + Drink2
err = error component. These reflect the portion of the measure that is not measuring the construct of interest, but rather some unknown or random phenomenon – hence error or disturbance.
P_internal = parent ratings of internalizing behaviour problems
pemoG3r = parent ratings of emotional disorder at Grade 3
pdpG3r = parent ratings of depression scale at Grade 3
P_external = parent ratings of externalizing behaviour problems
pphyG3r = parent ratings of physical aggression at Grade 3
phypG3r = parent ratings of hyperactivity at Grade 3
pindG3r = parent ratings of indirect aggression at Grade 3
podG3r = parent ratings of oppositional defiant behaviour at Grade 3
Q = the portion of the relationship between the internalizing and externalizing factors that is not accounted for by the smoking and drinking measures. It is unknown. It allows the internalizing and externalizing factors to be correlated without requiring that we account for the correlation between them using our measures. The magnitude of the relationship is quite large, and smoking and drinking cannot account for all that is going on there.
Both models have good fit (Teacher RMSEA = .048, CFI = .970, TLI = .950, Parent RMSEA = .054, CFI = .964, TLI = .942), with the parent fit appearing to be somewhat better than the teacher fit. Because this is an exploratory analysis, the parent model retains three non-significant paths with $p < .2$, to facilitate replication. All of the retained paths (path coefficients) in the teacher model are significantly greater than 0.

**Figure 5**
Teacher-Reduced Model

**Fit Index:**
CFI = .970  
TLI = .950  
RMSEA = .048

$\text{Drink}_1 =$ higher-risk drinking during pregnancy  
$\text{Drink}_2 =$ higher-risk drinking at 33 months  
$\text{Smoke}_1 =$ mother’s smoking during pregnancy  
$\text{Smoke}_2 =$ child exposed to second-hand smoking at 33 months  
$\text{Int}_1 =$ $\text{Smoke}_1 + \text{Drink}_1$  
$\text{Int}_2 =$ $\text{Smoke}_2 + \text{Drink}_2$  
$\text{err} =$ error component. These reflect the portion of the measure that is not measuring the construct of interest, but rather some unknown or random phenomenon – hence error or disturbance.

$\text{T\textunderscore internal} =$ teacher ratings of internalizing behaviour problems  
$\text{temoG}_3r =$ teacher ratings of emotional disorder at Grade 3  
$\text{tpvG}_3r =$ teacher ratings of passive victimization scale at Grade 3  
$\text{tphyG}_3r =$ teacher ratings of physical aggression at Grade 3  
$\text{thypG}_3r =$ teacher ratings of hyperactivity at Grade 3  
$\text{tindG}_3r =$ teacher ratings of indirect aggression at Grade 3  
$\text{tdelG}_3r =$ teacher ratings of delinquency at Grade 3  
$Q =$ the portion of the relationship between the internalizing and externalizing factors that is not accounted for by the smoking and drinking measures. It is unknown. It allows the internalizing and externalizing factors to be correlated without requiring that we account for the correlation between them using our measures. The magnitude of the relationship is quite large and smoking and drinking cannot account for all that is going on there.
6. Discussion

Alcohol is well established as a teratogenic substance (Streissguth, Landesman-Dwyer, Martin & Smith, 1980). Experimental animal studies have manipulated alcohol use to cause malformations among offspring; cross-sectional or correlational studies with humans have correlated the presence of similar malformations among infants to retrospectively measured maternal alcohol use during pregnancy; and longitudinal studies with prospective measures of alcohol use in pregnancy have confirmed those same malformations.

Quite sensibly, the early human research literature has been focused on large doses of alcohol and striking malformations in the faces of children (Huizink & Mulder, 2006; Jacobson & Jacobson, 2002; Richter & Richter, 2001). More recent research has focused on the less visible teratogenic effects of alcohol in humans. Problems with executive function – notably attention, impulsive behaviour and hyperactivity – have been demonstrated in correlational studies, as have other behaviour problems including antisocial and delinquent behaviour. Prenatal exposure to alcohol has been associated with internalizing behaviour problem, such as depression and anxiety. Deficits in cognitive functioning and learning are also evident among children with prenatal alcohol exposure, including memory and information-processing difficulties, poor problem-solving skills, impaired planning and response inhibition, lower IQ scores and problems with linguistic, perceptual and motor development.

Recent debate has been focused on dose effects. From a public health perspective, the question of how much alcohol, if any, is safe to drink during pregnancy has sparked substantial debate (Gijssen, Fulga, Garcia-Bourmessens & Koren, 2008; Kelly et al., 2009; Sayal, 2009).

The results of the first set of analyses (ANCOVA) presented above indicate that the children of mothers who report higher-risk drinking during pregnancy manifest a range of compromised developmental outcomes in early primary school compared with the children of mothers who reported lower-risk or no drinking during pregnancy. Out of a total of 79 different measures, 11 (14%) were significant at the 1% level. These negative outcomes occurred most frequently in the domain of children’s behaviour problems (6 of 22 measures), more specifically in higher ratings of aggressive and hyperactive behaviours by Junior Kindergarten (JK) teachers when the children were 4 years old, and again by Grade 3 teachers when the children were 8 years old. In contrast, parent ratings did not indicate significant negative effects of prenatal alcohol exposure on children’s behaviour problems.

The second domain of children’s functioning in which negative associations with prenatal alcohol exposure were evident was cognitive development/academic performance (4 of 23 measures). Statistically significant negative effects were found in auditory and memory performance on the DISC developmental task administered by trained researchers at 4 years of age, and poorer ratings by Grade 3 teachers on measures of children’s school preparedness, attitudes toward academics, and general academic functioning.

Animal studies have confirmed that the alcohol, tobacco has teratogenic effects on the nervous system of the fetus. Although the effects of prenatal tobacco exposure of birth weight and infant growth are well established, the effects on cognitive, behavioural and social/emotional functioning into childhood are less well documented (Cornelius & Day, 2007; Huizink & Mulder, 2006; Richter & Richter, 2001). In our findings, maternal
reports of smoking during pregnancy, collected when a child was 3 months old, were predictive of measurable problems in only one of five broad domains: child health (2 of 9 measures). Out of a total of 79 different measures, only 2 (2%) were significant at the 1% level. Since we would expect about 1% of the tests to be significant by chance alone; finding 2% of the tests to be significant is marginal evidence of an effect. Thus, for this approach to the analysis of data and given the large number of tests, we do not have conclusive evidence of smoking effects. A different statistical approach may give different results.

We also compared the children of women who reported both smoking and drinking during pregnancy with women who did neither (i.e. we left out the women who only smoked or only drank). The combined smoking and drinking was predictive in all five broad domains: general development (3 of 3 measures), cognitive development/academic performance (7 of 23 measures), social and emotional functioning (2 of 22 measures), behaviour problems (10 of 22 measures) and child health (2 of 9 measures). Out of a total of 79 different measures, 24 (30%) were significant at the 1% level. The apparent additive effect of the smoking and the drinking is intriguing, but must be interpreted cautiously given the possibility of selection bias. For example, women who smoke and drink during pregnancy may drink more than women who drink but do not smoke, or their nutritional status may be poorer, their body may already be coping with oxidative stress from smoking, or they may be living with a higher level of stress in their lives. In addition, people tend to smoke more when they are drinking.

Note that our use of statistical control techniques for 15 covariates would not have been sufficient to deal with such potential confounds.

The finding that the combination of prenatal exposure to both alcohol and tobacco predicted the most negative long-term effects on children in primary school is, however, consistent with the research literature that has reported that the negative effects of prenatal exposure to alcohol are increased when combined with other potentially harmful substances, including tobacco or non-prescription drugs (Fried, O’Connell & Watkinson, 1992; Fried & Watkinson, 1990).

- These findings also point to the importance of any future research to collect information about the use of multiple substances during pregnancy, in order to avoid inappropriate conclusions about the effects of one substance if no information on other substances is collected.

For example, if a study on maternal smoking during pregnancy does not collect information about the mothers’ drinking during pregnancy, and many of the smoking mothers also engaged in high-risk drinking, negative child outcomes may be attributed to prenatal exposure to tobacco when, in fact, they may be more strongly related to exposure to alcohol or the combination of the two substances.

Note also that the amounts of alcohol and tobacco use during pregnancy need not be large. Our criterion for smoking was “any smoking.” Our criterion for higher-risk drinking was a score of at least 1 on the CAGE scale. A score of 1 can be obtained by someone who feels badly about their drinking behaviour, who feels the need to cut back, or who has been criticized by others about their drinking.

Few studies of either prenatal alcohol use or smoking collect information on the use of both substances prenatally. For example,
Martin, Dombrowski, Mullis, Wisenbaker and Huttunen (2006) recently reported results from the Helsinki Longitudinal Project indicating that smoking during pregnancy was associated with several negative effects on children’s development at ages 5 and 12 years of age. The authors acknowledged in their conclusions that, “Smoking, drinking and other forms of drug use are correlated, and some of the resulting effects may have been related to maternal drug use during pregnancy. This study was unable to control for pregnancy drug and alcohol use, which is a clear limitation” (p. 499). The study of either prenatal smoking or alcohol use that does not include information on the use of both substances runs the risk of forming conclusions on the effect of one substance while the effects may result either from the use of the other substance, or, as in the present study, the negative effects of using both substances prenatally (see, for example, O’Connor & Paley, 2006).

Further, few studies control for other parent or family variables such as parent education, single-parent status or family income. Several studies have reported that both prenatal alcohol use and prenatal smoking are strongly related to these variables, so if they are not controlled in analyses, the subsequent child outcomes may be more a function of the child’s socio-economic environment after birth, than the smoking or alcohol use prenatally. Consistent with this concern are the findings of several studies that have reported no or much-reduced effects on children’s development of maternal prenatal smoking when socio-demographic factors and postnatal environment were controlled in the analyses (D’Onofrio et al., 2008; McGee and Stanton, 1994).

Several of the negative outcomes of prenatal alcohol abuse and smoking on children’s cognitive development at 33 and 48 months of
age were based on results of a standardized test of development administered to children individually by trained researchers. Nearly all of the other negative effects associated with maternal alcohol abuse and smoking during pregnancy occurred in ratings by the child’s teacher at 4 and 8 years of age. The fact that teachers would not have been aware of the mothers’ smoking or drinking behaviour prenatally or when the (now about 8 years old) child was 33 months old strengthens the confidence one can place on these results. The ratings collected from the children’s parents, on the other hand, showed virtually no association between the mother’s prenatal drinking or smoking and children’s later behaviour in the ANCOVA analyses.

The finding of larger effects in teacher report data than in parent report data is consistent with the literature (Brown et al., 1991). Several interpretations of the different results between teacher and parent ratings are possible. One of many is that teacher ratings of children’s behaviour and academic performance are generally considered to be more valid than those of parents, because teachers have extensive experience observing many children whereas parents’ experience is typically much more limited in this regard. Parents are not able to compare their child’s behaviour with those of many other children, while teachers are constantly making such comparisons. Also, since many of the child behaviour problems rated by both parents and teachers involve difficulties in relationships with peers, teachers would have more opportunity to observe a child’s peer interactions than parents. Finally, the negative outcomes in the area of academic performance were based on ratings of the child’s behaviour in the classroom setting, ratings that can be collected only from teachers since parents have no or extremely limited opportunity to observe such behaviours.

The fact that significant effects were present in the teachers’ rating when children were age 4 (Junior Kindergarten) and age 8 (Grade 3) but not age 6 (Grade 1) may reflect the fact that children face major developmental transitions at ages 4 and 8. At 4 and 5 years of age, individual differences in children’s school readiness are viewed as resulting from different levels of maturity in cognitive and social development. The challenges of formal school entry at this age accentuate individual differences in children’s social and cognitive maturity. The finding that children whose mothers reported higher-risk drinking during pregnancy, and particularly if they also reported smoking, showed compromised cognitive development and elevated levels of hyperactive and aggressive behaviours may reflect their delayed social and cognitive development and difficulty in adapting successfully to the challenges of formal school entry at age 4.

At age 7, another major transition begins in normal cognitive development, namely the transition to conceptual thinking or, in Piagetian terminology, concrete operational thought (Piaget, 1964). Delays in cognitive development at this age mean that children cannot successfully adapt to academic tasks requiring the use of concepts in mathematics and reading, resulting in poor school performance and possible frustration and conflict with more mature peers. Consequently, the negative effects on children’s cognitive and social development of prenatal exposure to alcohol and tobacco may be particularly noticeable by teachers at this age.

In the second set of analyses, we used a structural equation modelling technique to address some of the issues not dealt with in the more coarse-grained ANCOVA analyses reported above. We selected a subset of variables measured in Grade 3 that are related to problems in social and emotional function for dependent variables, and we included measures of drinking and smoking exposure at two times in the children’s development – in utero and when the child was 33 months old. The use of the intermediate measures of smoking and drinking behaviour act as a general control for the
“third variable problem.” If something that we have not measured is related to both our predictor and our outcome measure, we can get a spurious relationship mediated by that unseen variable. However, if such a variable exists, the spurious effect ought to be more powerful when the smoking or drinking was measured at 33 months of age than when measured at 3 months of age. The more recent measurement ought to “carry” the third variable effect more strongly than the more distant measure.

When we examine the measures of child behaviour collected from teachers, there is clear support for the hypothesis that drinking during pregnancy leads to problems in social and emotional functioning in elementary school, with significant paths from reported drinking during pregnancy and both internalizing behaviours ($r = .19$) and externalizing behaviours ($r = .21$). The more proximal measure of maternal drinking when the child was 33 months old does not predict either externalizing or internalizing behaviour. Smoking during pregnancy does predict externalizing behaviour problems ($r = .13$) and exposure to second-hand smoke at 33 months does predict internalizing behaviour ($r = .15$). If we interpret this at face value, it suggests that the mother’s smoking behaviour during pregnancy can have effects that are evident 8 years later in a child’s classroom behaviour and that those effects are over and above the effects of more recent (albeit 4 or 5 years ago) exposure to second-hand smoke. Given that the effects of paths are additive, the effect of smoking and drinking combines for an essentially doubled effect on teacher-rated externalizing behaviour.

As with the first set of analyses (ANCOVA), the same analysis using measures of child behaviour collected from parents shows fewer effects. Only smoking during pregnancy is a significant predictor of externalizing behaviour ($r = .17$).

Structural equation modelling is a correlational technique. While it is a truism that correlation does not prove causation, the findings of our two models interact with the existing literature in a powerful manner. Drinking and smoking during pregnancy are significant predictors of problems in externalizing behaviour noted 8 years later by both teachers and parents and of internalizing behaviour noted by teachers. These predictors are significant even when “competing” for covariance with related measures collected much closer in time to the behaviour data collection. In the context of recent animal and human findings, the most responsible interpretation of these findings is that smoking and drinking during pregnancy cause some problems in Grade 3 and the predictive relationships observed in the SEM is due to the causal impact of tobacco and alcohol use during pregnancy.

How big is the effect we are looking at? Is it merely statistical, or is it of a magnitude that people would notice?

One way to approach this problem is to look at comparative effect sizes. Meyer et al. (2001) presented an array of effect sizes from meta-analyses that allow a researcher to fit a finding onto a scale. In the table below, our own findings have been embedded among other effect size findings, using the $r$ statistic to make them more compatible with the results of SEM. For example, when people with allergic reactions use antihistamines for runny nose and sneezing, the effect size averages 0.11. Prenatal smoking has an effect of .13 on externalizing ratings. If our data are accurate, then abstinence from smoking and drinking during pregnancy ought to have an effect on internalizing behaviour about as powerful as taking non-steroidal anti-inflammatory drugs (NSAIDS) for pain or taking anti-histamines for allergies. Given that the effects of prenatal smoking and drinking are both evident in teacher reports, the effect of the double abstinence may be twice as large. Moreover, there may be another independent relationship with second-hand
smoke. Keep in mind that causal inference from a SEM of this type must be cautious in the absence of manipulation of the independent variable.

Data (effect sizes) from the first statistical analysis of this report (i.e. the ANCOVA results) are reported in terms of the d statistic rather than the r statistic. We looked for meta-analytic studies not included in Meyer et al.’s (2001) article that would expand the range of comparators for our results.

Bhutta, Cleves, Casey, Cradock and Anand (2002) reported a meta-analysis of the cognitive and behavioural outcomes of children who were born preterm. When we interpolate from their measure of weighted mean difference (WMD) by dividing by the theoretical standard deviation of the ability test scores, they demonstrate a mean d of about 0.72 for cognitive measures. Thus, the preterm children in the studies they found were about 11 IQ points or .7 standard deviations below the comparator children born at term. This effect is proportional to gestational age (r = .71), showing an increase in the WMD of roughly .67 points or in the d statistic of about .044 per week of prematurity. Our observed mean d statistics for measures of general child development (see Appendix 1) were -.29 for prenatal maternal tobacco use, -.28 for prenatal maternal alcohol use and -.57 for the difference between children of mothers who used both substances and mothers who used neither. Thus our observed d statistics correspond to those observed in Bhutta, Cleves, Casey, Cradock and Anand’s (2002) study at roughly 6,6 and 13 weeks of prematurity for tobacco, alcohol and joint exposure, respectively. In rough terms, smoking and drinking during pregnancy even at the relatively low levels found in our sample seem to be the equivalent of 6 weeks of prematurity – per substance used.

Schachter, Pham, King, Langford and Moher (2001) conducted a meta-analysis of the effects of Ritalin on children and adolescents with ADHD. In general, they found that the medication was effective based on an array of behavioural measures, but noted that the effects as reported by teachers were stronger than those reported by parents. These researchers reported a mean effect size of .78 for teacher reports and .54 for parent reports. Our results for behavioural problem reports showed effect sizes for teachers of .29, .40 and .70 and for parents of .21, .12 and .25 for prenatal tobacco exposure, alcohol exposure and the combined exposure, respectively.

Paolucci and Violato (2004) reported a meta-analysis on the effects of child sexual abuse. These authors reported a variety of weighted mean effect sizes for diagnoses ranging from
The effect size for academic performance was .19. This compares with our effect sizes for all measures of academic and cognitive performance of \(-.09, -.26\) and \(-.37\) for prenatal tobacco exposure, alcohol use and the combined use, respectively. (See Appendix 1.)

Kitzmann, Gaylord, Holt and Kenny (2003) reported a meta-analysis of the effects on children of witnessing domestic violence. On a variety of problems (internalizing, externalizing, social, academic and other), they reported a mean effect size of .40 when comparing children who witnessed violence with those who did not. Our mean d statistics for measures of general development (see Appendix 1) were \(-.29\) for prenatal maternal tobacco use, \(-.28\) for prenatal maternal alcohol use and \(-.57\) for the difference between children of mothers who used both substances and mothers who used neither.

These findings help to put the measured effects of smoking and drinking into perspective. When we compare the effects we found with those observed with three predictors of worse performance (prematurity, witnessing domestic violence and child sexual abuse), there was a strong overlap. When we compare with intervention for ADHD with Ritalin, the effects of combined prenatal substance use are roughly comparable (but reversed in sign) to the impact of Ritalin on behavioural measures. In broad terms, the impact of the substances appears to be comparable to moderate prematurity (6 weeks for each substance, 12 for both), child sexual abuse (either substance, or twice the magnitude if both were used), or witnessing domestic violence (less impact for one substance, greater impact for combined). The impact of ADHD that is reversible by using Ritalin appears to be roughly comparable to use of both substances.

While these comparisons to meta-analytic findings must be considered approximate, they do give a sense of scale. In our sample, the impact of smoking and drinking during pregnancy is of a magnitude that compares with prematurity, sexual abuse, witnessing domestic violence and the Ritalin-reversible effects of ADHD. It is also important to note that these are aggregate findings, and it is hard to imagine that every child would show the same magnitude of effects – there will be lots of variation.

In conclusion, the results of the present study suggest that children whose mothers report higher-risk alcohol consumption during pregnancy show long-term negative outcomes in measures of school performance and behaviour problems compared with mothers who report lower-risk drinking. These problems are accentuated in children whose mothers also report smoking during the pregnancy. Further, the negative effects are most apparent when children are 4 years of age, and faced with the challenges of formal school entry (i.e. poor school readiness), and again at age 8, when individual differences in conceptual thinking may be particularly salient to teachers. The percentage of measures reflecting the disadvantage of children exposed to prenatal alcohol and tobacco increased from 37% at age 4 to 47% at age 8. If this pattern continues, the negative effects on children’s academic and social behaviour may continue to be compromised as they enter early adolescence; that is, prenatal exposure to maternal high-risk drinking and smoking may be linked to disrupted cognitive and social development at critical periods in children’s development, with lifelong consequences.


Appendix 1

Effects of Alcohol and Tobacco During Pregnancy: Summary Results (p-values and effect sizes)

- **Note**

  *A negative sign (−) indicates poorer outcomes on the measure associated with prenatal exposure to tobacco and/or high-risk drinking; a positive sign indicates a better outcome on the measure associated with prenatal exposure to tobacco and/or high-risk drinking.*

  *Statistically significant results are shown in bold.*

### Outcome Variables

<table>
<thead>
<tr>
<th>Sample size (n)</th>
<th>Prenatal Exposure to Tobacco (PET): 0 = not exposed, 1 = exposed</th>
<th>Mother High-Risk Drinker (MHRD): 0 = no, 1 = yes</th>
<th>Interaction: not exposed, not high-risk drinker vs. exposed, high-risk drinker</th>
</tr>
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<tbody>
<tr>
<td>General Child Development</td>
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<td></td>
<td></td>
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<tr>
<td>1 DISC – overall development quotient, 33 months</td>
<td>404</td>
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<td>−0.34</td>
</tr>
<tr>
<td>2 DISC – overall development quotient, 48 months</td>
<td>427</td>
<td>−0.19</td>
<td>−0.31</td>
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<td>3 ABC – maturity/school-readiness scale, 48 months</td>
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<td>−0.47</td>
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</tr>
<tr>
<td>Mean effect sizes</td>
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<td></td>
</tr>
<tr>
<td>Cognitive Development/Academic Performance</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4 DISC – auditory and memory development quotient, 33 months</td>
<td>404</td>
<td>−0.19</td>
<td>−0.34</td>
</tr>
<tr>
<td>5 DISC – auditory and memory development quotient, 48 months</td>
<td>427</td>
<td>−0.19</td>
<td><strong>−0.44</strong></td>
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<td>6 PPVT W-ability, 48 months</td>
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<td>−0.12</td>
<td>−0.33</td>
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<tr>
<td>7 WPPSI Block Design – Standardized Score, 48 months</td>
<td>424</td>
<td>−0.36</td>
<td>−0.11</td>
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<td>8 Teacher rated: student-preparedness scale, Grade 1</td>
<td>282</td>
<td>−0.15</td>
<td>−0.25</td>
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<td>9 Child’s attitudes toward academics scale, Grade 1</td>
<td>285</td>
<td>−0.02</td>
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<tr>
<td>10 Teacher rated: academic functioning scale, Grade 1</td>
<td>285</td>
<td>−0.12</td>
<td>−0.15</td>
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<tr>
<td>11 Teacher rated: adaptive functioning scale, Grade 1</td>
<td>285</td>
<td>+0.02</td>
<td>−0.42</td>
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</table>
## Outcome Variables

<table>
<thead>
<tr>
<th></th>
<th>Sample size (n)</th>
<th>Prenatal Exposure to Tobacco (PET): 0 = not exposed, 1 = exposed</th>
<th>Mother High-Risk Drinker (MHRD): 0 = no, 1 = yes</th>
<th>Interaction: not exposed, not high-risk drinker vs. exposed, high-risk drinker</th>
</tr>
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<tbody>
<tr>
<td>12</td>
<td>Parent reported: child repeated a grade, Grade 1</td>
<td>345</td>
<td>+0.05</td>
<td>+0.19</td>
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<tr>
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<tr>
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<tr>
<td>18</td>
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<tr>
<td>19</td>
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<tr>
<td>20</td>
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<td>+0.06</td>
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<tr>
<td>21</td>
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<td>22</td>
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<td>EQAO – writing, Grade 3</td>
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<td>Mean effect sizes</td>
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### Outcome Variables

#### Social/Emotional Functioning

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<th>Interaction: not exposed, not high-risk drinker vs. exposed, high-risk drinker</th>
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</thead>
<tbody>
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Mean effect sizes: -0.08, -0.18, -0.26
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<th>Mother High-Risk Drinker (MHRD): 0 = no, 1 = yes</th>
<th>Interaction: not exposed, not high-risk drinker vs. exposed, high-risk drinker</th>
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<td>−.52</td>
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<td>−.36</td>
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</tr>
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</tr>
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<td>55 Parent rated: OCHS oppositional defiant scale, Grade 1</td>
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<td>−.08</td>
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<td>Mean effect sizes</td>
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<td>−0.25</td>
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## Outcome Variables

### Child Health

<table>
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<tr>
<th></th>
<th>Description</th>
<th>Sample size (n)</th>
<th>Prenatal Exposure to Tobacco (PET): 0 = not exposed, 1 = exposed</th>
<th>Mother High-Risk Drinker (MHRD): 0 = no, 1 = yes</th>
<th>Interaction: not exposed, not high-risk drinker vs. exposed, high-risk drinker</th>
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</thead>
<tbody>
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<td>71</td>
<td>Parent-reported child's health, 48 months</td>
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<td>+0.01</td>
<td>-0.14</td>
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<td>72</td>
<td>Child's height, 48 months</td>
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<td>+0.01</td>
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<td>-0.09</td>
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<td>-0.07</td>
<td>+0.01</td>
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<td>77</td>
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<td>-0.13</td>
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<td>78</td>
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<td>+0.08</td>
<td>-0.13</td>
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<td>+0.15</td>
<td>-0.49</td>
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Mean effect sizes: -0.14, -0.01, -0.16

Mean of all effect sizes in Appendix 1: -0.15, -0.21, -0.36
Appendix 2

Variables Employed as Covariates

The following covariates were used as control variables in all analyses:

- Sex of respondent (male, female)
- Sex of child (male, female)
- Respondent’s year of birth (year)
- Child has any sibling (yes, no)
- Respondent ever married (yes, no)
- Respondent in common-law union (yes, no)
- Single parenthood (yes, no)
- Respondent’s education (years of schooling)
- Respondent working full time (yes, no)
- Respondent working part time (yes, no)
- Respondent in labour force (yes, no)
- Household monthly income ($)
- Immigration status (immigrant, born Canadian)
- Anglophone (yes, no)
- Francophone (yes, no)
### CHILDREN’S GENERAL DEVELOPMENT

#### At 33 months of age

**Developmental Inventory for Screening Children (DISC): Overall Development Quotient**

<table>
<thead>
<tr>
<th>Group</th>
<th>Means</th>
<th>Std. Error</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal Exposure to Tobacco (PET)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not exposed</td>
<td>100.24</td>
<td>1.36</td>
<td>278</td>
</tr>
<tr>
<td>Exposed</td>
<td>97.66</td>
<td>1.39</td>
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<tr>
<td>Mother Higher-Risk Drinker (MHRD)</td>
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<tr>
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<td>PET and MHRD</td>
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<td></td>
<td></td>
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<td>Not exposed, not higher-risk drinker</td>
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<td>Exposed, higher-risk drinker</td>
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#### At 48 months of age

**DISC Overall Development Quotient**

<table>
<thead>
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<th>Means</th>
<th>Std. Error</th>
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<tbody>
<tr>
<td>Prenatal Exposure to Tobacco (PET)</td>
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</tr>
<tr>
<td>Not exposed</td>
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<td>Mother Higher-Risk Drinker (MHRD)</td>
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<td>PET and MHRD</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Not exposed, not higher-risk drinker</td>
<td>98.35</td>
<td>0.72</td>
<td>274</td>
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<td>91.89</td>
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### ABC School Readiness

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<tr>
<td>Not exposed</td>
<td>26.35</td>
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### CHILDREN’S COGNITIVE DEVELOPMENT/ACADEMIC PERFORMANCE

#### At 48 months of age

### DISC Auditory and Memory Development Quotient

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<th>Std. Error</th>
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<tr>
<td>Not exposed</td>
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<td>0.83</td>
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<td>91.69</td>
<td>2.24</td>
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<td>PET and MHRD</td>
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<td></td>
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<tr>
<td>Not exposed, not higher-risk drinker</td>
<td>98.15</td>
<td>0.90</td>
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<td>88.69</td>
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### At Grade 3

#### Teacher-Rated Student Preparedness Scale

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#### Teacher-Rated Child’s Attitudes Toward Academics Scale

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<tr>
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<td>0.73</td>
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<td><strong>PET and MHRD</strong></td>
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#### Teacher-Rated Child’s Academic Functioning Scale

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<tr>
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## Teacher-Rated Child’s Adaptive Functioning Scale

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<td>0.39</td>
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## Parent-Reported Child Suspended from School (%)

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## Teacher-Reported Child Received Special Education/Services (%)

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<td>0.088</td>
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<td>0.038</td>
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# CHILDREN’S SOCIAL/EMOTIONAL FUNCTIONING MEASURES

## At Grade 3

### Teacher-Rated Emotional Disorder Scale

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<tr>
<td>Not exposed</td>
<td>4.78</td>
<td>0.66</td>
<td>155</td>
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<tr>
<td>Exposed</td>
<td>5.31</td>
<td>0.50</td>
<td>87</td>
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<tr>
<td><strong>Mother Higher-Risk Drinker (MHRD)</strong></td>
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<tr>
<td>No</td>
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<td>6.23</td>
<td>0.77</td>
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<td>Not exposed, not higher-risk drinker</td>
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### Teacher-Rated Conflict Management Scale

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<tr>
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<tr>
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<tr>
<td>Not exposed, not higher-risk drinker</td>
<td>15.40</td>
<td>0.24</td>
<td>149</td>
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<tr>
<td>Exposed, higher-risk drinker</td>
<td>13.62</td>
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## CHILDREN’S HEALTH MEASURES

### At Grade 1

#### Child Exposed to Second-Hand Smoke

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<td>No</td>
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<td>0.77</td>
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<tr>
<td>Not exposed, not higher-risk drinker</td>
<td>4.43</td>
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### At Grade 3

#### Child Exposed to Second-Hand Smoke

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<tr>
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<td>4.21</td>
<td>0.84</td>
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<td>10.81</td>
<td>2.64</td>
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# CHILDREN’S BEHAVIOUR PROBLEMS MEASURES

**At 48 months of age**

## Teacher-Rated Disruptiveness Scale

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<tr>
<td>Not exposed</td>
<td>6.78</td>
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<td>185</td>
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<td>Exposed</td>
<td>8.70</td>
<td>0.89</td>
<td>84</td>
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<td>Mother High-Risk Drinker (MHRD)</td>
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<td>PEN and MHRD</td>
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<tr>
<td>Not exposed, not high-risk drinker</td>
<td>5.71</td>
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## Teacher-Rated Hyperactivity Scale

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<td>3.99</td>
<td>0.28</td>
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### Teacher-Rated Indirect Aggression Scale

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<tr>
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### Teacher-Rated Physical Aggression Scale

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<td>0.40</td>
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<tr>
<td>Exposed</td>
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<td>0.39</td>
<td>87</td>
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<td>2.81</td>
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<tr>
<td>PEN and MHRD</td>
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<tr>
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### At Grade 1

**Teacher-Rated Delinquency Scale**

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<td></td>
</tr>
<tr>
<td>Not exposed</td>
<td>0.93</td>
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<tr>
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<tr>
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<td>0.59</td>
<td>0.11</td>
<td>176</td>
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<tr>
<td>Exposed, high-risk drinker</td>
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### At Grade 3

**Parent-Rated Physical Aggression Scale**

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<th>Means</th>
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<tr>
<td>Not exposed</td>
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<td>Exposed</td>
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<tr>
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<td>2.46</td>
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<tr>
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<tr>
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<td>1.61</td>
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### Teacher-Rated Hyperactivity Scale

<table>
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<th>Means</th>
<th>Std. Error</th>
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<tbody>
<tr>
<td>Prenatal Exposure to Nicotine (PEN)</td>
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</tr>
<tr>
<td>Not exposed</td>
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<td>Exposed</td>
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<tr>
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<td>4.55</td>
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<td>Yes</td>
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<td>PEN and MHRD</td>
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<td></td>
<td></td>
</tr>
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<td>Not exposed, not high-risk drinker</td>
<td>4.14</td>
<td>0.35</td>
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</tr>
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<td>Exposed, high-risk drinker</td>
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<td>1.01</td>
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### Teacher-Rated Indirect Aggression Scale

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<td>Prenatal Exposure to Nicotine (PEN)</td>
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<td></td>
<td></td>
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<tr>
<td>Not exposed</td>
<td>1.83</td>
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### Teacher-Rated Physical Aggression Scale

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<tbody>
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</tr>
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</tr>
<tr>
<td>Exposed</td>
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<td>0.39</td>
<td>89</td>
</tr>
<tr>
<td>Mother High-Risk Drinker (MHRD)</td>
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<td>217</td>
</tr>
<tr>
<td>Yes</td>
<td>3.58</td>
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</tr>
<tr>
<td>PEN and MHRD</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Not exposed, not high-risk drinker</td>
<td>1.57</td>
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<td>146</td>
</tr>
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<td>Exposed, high-risk drinker</td>
<td>3.85</td>
<td>0.68</td>
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### Teacher-Rated Delinquency Scale

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<th>Means</th>
<th>Std. Error</th>
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</tr>
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<tbody>
<tr>
<td>Prenatal Exposure to Nicotine (PEN)</td>
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<tr>
<td>Not exposed</td>
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</tr>
<tr>
<td>Exposed</td>
<td>1.68</td>
<td>0.24</td>
<td>80</td>
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<tr>
<td>Mother High-Risk Drinker (MHRD)</td>
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</tr>
<tr>
<td>No</td>
<td>0.84</td>
<td>0.20</td>
<td>205</td>
</tr>
<tr>
<td>Yes</td>
<td>1.96</td>
<td>0.36</td>
<td>23</td>
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<tr>
<td>PEN and MHRD</td>
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<td></td>
</tr>
<tr>
<td>Not exposed, not high-risk drinker</td>
<td>0.78</td>
<td>0.14</td>
<td>141</td>
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<tr>
<td>Exposed, high-risk drinker</td>
<td>2.47</td>
<td>0.42</td>
<td>16</td>
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Early primary school outcomes

associated with maternal use of alcohol and tobacco during pregnancy
and with exposure to parent alcohol and tobacco use postnatally
For over 20 years, an extensive body of research has documented significant neurodevelopmental deficits in individuals with Fetal Alcohol Spectrum Disorders or FASD (Mattson et al., 1998; Streissguth et al., 1991). FASD is an umbrella term that includes three conditions involving brain damage and associated central nervous system impairment: Fetal Alcohol Syndrome (FAS), Partial FAS, and Alcohol Related Neurodevelopmental Disorder (ARND). This impairment involves primary neurocognitive disabilities such as cognitive deficits, memory problems, attention deficits and hyperactivity, speech and language impairment, internalizing and externalizing behavior problems, and deficits in executive, social, and adaptive functioning (CDC, 2004).

Due to an interaction between these primary disabilities and adverse environmental experiences, individuals with FASD who do not receive appropriate interventions in childhood struggle with serious secondary disabilities (Carmichael Olson et al., 1999; Streissguth & O'Malley, 2000). For example, children with FASD are at significant risk of learning disabilities and classroom behavior problems (Carmichael Olson et al., 1992; Mattson et al., 1998) and, ultimately, school disruption (Streissguth et al., 1996). Adolescents with FASD also are at increased risk for mental health problems, alcohol and substance abuse problems, sexual misconduct, and delinquency and juvenile commitment (Streissguth et al., 1996, 2004).

Although researchers have long recognized that in order to reduce the risk for secondary disabilities, early diagnosis and disability—targeted interventions are necessary throughout childhood and beyond (e.g., Streissguth et al., 1996, 2004), only a few FASD interventions have been developed at this point. Several of these treatments have been empirically tested in randomized control studies and show positive, albeit short-term, efficacy with respect to targeting specific skill deficits in alcohol exposed children.

Parenting Skills Training

In the Parent and Child Assistance Program (PCAP; Grant et al., 2004) at the University of Washington, paraprofessionals in advocate case manager roles worked with 19 young women diagnosed with FASD conditions to connect them with appropriate services, teach them how to access services for themselves and their children, and support their ability to provide a safe caregiving environment for their children. Results of this 12-month community pilot intervention indicated improved outcomes (including reduced substance use, increased contraception use, increased use of medical/mental healthcare services, and stable housing). The researchers concluded that services of this nature might contribute to the prevention of additional alcohol-exposed pregnancies.

In an intervention (Families Moving Forward; FMF) based generally upon parenting training programs with documented efficacy in families with non-alcohol exposed children, researchers (Olson et al., 2005) designed an intervention aimed at improving caregiver self-efficacy and reducing problem behaviors in children with FASD. Caregivers were taught two skills: 1) how to change unproductive cognitions and attitudes ("reframing") from a perspective that viewed child disobedience as willful to a perspective that viewed child disobedience as a byproduct of brain damage, and 2) how to substitute reactive punitive responses with positive behavior reinforcement. The study sample involved 52 children 5-11 years of age and their caregivers. At enrollment, all child participants had clinically significant externalizing problems or attention deficits, as measured by standardized assessment procedures. The intervention involved 16+ sessions of supportive behavioral consultation on a biweekly basis. Post-treatment results indicated that compared with caregivers in a community standard of care group, caregivers involved in the FMF intervention experienced a significantly improved sense of parenting self-efficacy, perceived that their family
needs were met more often, and reported a significantly decreased number of disruptive behavior problems in their children. The researchers concluded that the FMF model showed initial promise with respect to improving caregiving practices and reducing child disruptive behaviors.

Bertrand (2009) reviewed a University of Oklahoma study that compared two evidence-based FASD interventions designed to decrease behavior problems in children and reduce parenting stress. One treatment, based on an adaptation of Parent-Child Interaction Therapy or PCIT (Eyberg & Boggs, 1998), involved in vivo coaching of targeted parenting skills with parents and children. The other intervention involved a parent-only Parenting Support and Management (PSM) program that incorporated components of other generally effective behavioral modification programs. The study sample involved 58 children ages 3-7 with FASD diagnoses and their caregivers. The intervention was delivered in 14 weekly 90-minute sessions of caregiver training for both study groups. In addition, the PCIT group received conjoint parent-child sessions. Overall, significant improvements in parent distress and reduced child behavior problems were found in both intervention groups, with no significant differences in outcomes between the two groups. According to Bertrand (2009), these results suggested that caregivers of children with FASDs could benefit from both relationship-focused and behaviorally oriented interventions.

Early Education Interventions

In the first systematic study to test a school-based FASD intervention, Adnams and colleagues (2007) demonstrated the efficacy of school-based language and literacy training (LLT) in a group of South African elementary school children. The intervention involved phonological awareness training and teaching of pre- and early literacy skills necessary for reading and spelling competency. The study sample involved 40 children with FASD, all age 9, who were randomly assigned to either the intervention condition or a control group. A third group of non-exposed children were assigned to another control group. Outcome measures involved standardized tests, questionnaires administered to teachers and parents, and classroom observations. Both at baseline and at the conclusion of the nine-month intervention, subjects with FASD were significantly weaker than nonexposed children in tests of early literacy tests and in a teacher-rated assessment of adaptive behaviors. Although average post-treatment test scores for prenatally exposed children remained lower than their nonexposed peers, post-intervention academic and literacy scores for all groups showed improvement. Moreover, there were significantly greater improvements in the FASD intervention group compared to the FASD control group on academic and literacy measures.

In a math learning readiness intervention, a research group in Georgia (Kable et al., 2007) assessed whether a consistent method of instruction across therapeutic, home, and school environments could improve mathematic skills and behavioral problems. The intervention involved the teaching of learning strategies to compensate for FASD-associated visual-spatial processing problems and executive function deficits (e.g., learning ability and working memory) that manifested in poor math and pre-math skills. The study involved 56 children ages 3-10 with a diagnosis of either FAS or Partial FAS. All subjects received educational support, including a neurodevelopmental assessment, as well as guidance to their caregivers on how to obtain appropriate educational placements and individualized education plans. Caregiver education, case management services, and psychiatric consultation also were used to support learning readiness. Children in the intervention group received six sessions of individualized instruction while their caregivers received training on how to support their children’s learning readiness by incorporating math concepts into free play, providing structured mathematical activities to their child, and facilitating completion of math homework. Compared to the control group, the intervention group made greater gains on math outcome measures, and these gains were maintained at a six-month follow-up (Coles et al., 2009). Positive gains also were made with respect to a reduction in child behavior problems. These results suggested to the researchers that a psychoeducational program that targeted specific neurodevelopmental deficits could help remediate math learning deficits.

In a study aimed at reducing the working memory deficit commonly seen in children with prenatal alcohol exposure, Loomes and colleagues (2008) developed an intervention that trained children in using rehearsal techniques to recall numbers prior to a digit span task administered in three different trials (pre-intervention, immediately following the brief intervention, and approximately 10 days after the intervention with an intervention "reminder"). The study involved 33 prenatally exposed children ages 4-11. Compared to the control group, the intervention group showed a significant increase in recall on the digit span task given 6-21 days after the training.

Neurodevelopmental Habilitation

Children with FASD are viewed by caregivers and teachers as having significantly poorer social skills (e.g., failure to consider the consequences of actions, difficulty understanding social cues, indiscriminant social behavior, poor choices in peer relationships, and difficulty communicating in social contexts) than their non-impaired peers, even after controlling for differences in cognitive functioning (Mattson et al., 1999), and these skill deficits continue into adulthood (Streissguth, 1997). In the first systematic evaluation of a treatment designed to improve the social functioning of children with FASD, O’Connor and colleagues (2006) adapted an evidence based parent-assisted social skills intervention called Children’s Friendship Training (CFT; Frankel & Myatt, 2003) to address the social, cognitive, and behavioral impairments common among children with FASDs. CFT teaches children how to interact with peers, how to enter a group of children already playing, how to arrange and handle in-home play dates, and how to avoid and work out conflicts. Caregivers are trained in how to assist their children with these skills. In this study, 100 children with FASD between 6-12 years of age were randomly assigned to either an intervention group or a delayed treatment (control) group. Children in the intervention group received 12 weekly 90-minute sessions of training, and caregivers attended separate concurrent sessions where they received education on FASD and were instructed on the social skills their children were learning. Skill training included simple didactic rules of social behavior, modeling, rehearsal, and performance feedback during treatment sessions, in-home rehearsals, homework assignments, and caregiver coaching during play between children. Results indicated that compared to the control group, those in the intervention group showed statistically significant improvement in their knowledge of appropriate social behavior, made gains in social skills, and decreased their problem behaviors. These improvements were maintained over a three-month follow-

continued on page 16
Impaired executive functioning is a central deficit for children with FASD (Mattson et al., 1998). In fact, many of the learning and social/emotional/behavioral difficulties displayed by children with FASD stem from underlying deficits in executive functioning (Connor et al., 2000). Executive functioning involves specific cognitive skills such as processing, organizing, and sequencing of information; goal-directed planning, cause and effect analysis, and cognitive flexibility; and emotion control and response inhibition. Deficits in executive functioning can be particularly devastating as these skills affect virtually all aspects of human behavior and adaptive functioning. In a systematic study to explore the efficacy of executive skills training for children with FASD, Chasnoff and colleagues (2009) developed an intervention adapted from the Alert Program© (Williams & Shellenberger, 1996) that involves strategies for improving memory, cause and effect reasoning, sequencing, planning, and problem solving. A total of 78 children with FASD between ages 6-11 participated in the study. Those in the intervention group received 12 weekly neurocognitive habilitation group therapy sessions while their parents simultaneously participated in a parent education group. The control group received referrals for community-based services such as occupational therapy, physical therapy, or speech and language therapy. Baseline and outcome assessment was based on standardized measures. Results indicated that compared to the control group, children who received the intervention showed significant improvement in executive functioning skills.

In another behavioral intervention, Vernescu (2007) examined whether Attention Process Training could improve the executive functioning of children with FASD. In this study, 20 Inuit children with FASD ages 6-11 were randomly assigned to either the intervention group or a control group. Both groups were seen for 12 30-minute sessions over 3 weeks, with the control group playing games and receiving academic support during those sessions. Baseline and post-intervention assessment involved standardized measures of attention, nonverbal reasoning ability, and teacher-completed behavioral measures of attention and executive function. Results indicated that children in the intervention group showed significant improvement on measures of sustained attention and non-verbal reasoning ability, but there was no improvement on measures of executive function.

In a computer-based intervention to increase safety skills (Coles et al., 2007), 32 children with FASD ages 4-10 were randomly assigned to one of two intervention groups and taught computer-administered safety rules and behavioral sequences involving either a fire in their home or crossing a city street. Each intervention group served as the control group for the alternate intervention. Results indicated that compared to controls, children in both intervention groups showed significant gains in safety-related knowledge and appropriate behavioral responses.

Pharmacological Interventions
In one of the first studies to investigate the impact of medication on FASD symptoms (Snyder et al., 1997), 12 children ages 6-16 with FAS and ADHD and positive response to stimulants were administered stimulant versus placebo. Results indicated significant improvement in hyperactivity with the stimulant medication per parent report but no significant effects for attention or impulsivity.

In 1998, a small randomized double-blind cross-over study (Osterheld et al., 1998) involving four Native American children ages 5-12 with FASD tested the effects of Methylphenidate versus placebo and vitamin. Results indicated no significant differences on measures of attention.

In a more recent study, a retrospective chart review of 27 youngsters ages 5-14 with FASD found “normalization” in up to 70 percent of the sample with respect to hyperactivity/impulsivity and opposition/defiance symptoms but in only 33 percent of the sample with regard to inattention (Doig, McClellan, & Gibbard, 2008). Results of this study contrasted with a previous study (O’Malley, Koplin, & Dohner, 2000), which found a preferential improvement in ADHD symptoms with dextroamphetamine (79 percent of 19 subjects) versus methylphenidate (22 percent of 23 subjects). Noting the contrasting findings in the two studies, Doig and colleagues (2008) concluded that a clearly identified preferential stimulant choice for children with FASD and ADHD had not yet been identified.

Only one study to date has investigated the efficacy of a combined intervention involving the impact of medication on psychosocial treatment (i.e., children’s friendship training). In a well-designed study involving children with FASD, Frankel and colleagues (2006) randomly assigned 77 children ages with FASD ages 6-12 to one of four conditions: a group that received stimulant medication, a group that received neuroleptic medication (i.e., risperidone for 11 of 13 children, with the other two receiving olanzapine), a group that received both medications, and a group that received no medications. Following 12 sessions of Children’s Friendship Training, results indicated that compared to all other groups, children prescribed neuroleptic medication showed greater social skills improvements in response to CFT on all standardized social outcome measures (parent and teacher ratings). In contrast, children prescribed stimulant medication either failed to show any improvement or showed poorer outcomes than children who did not receive stimulants. The researchers noted that the results of this study contrasted with their earlier study (Frankel, Myatt, & Cantwell, 1995) which showed a beneficial effect from stimulant medications given concurrently with CFT in children with ADHD.

Summary
Peadon and colleagues (2009) noted in their systematic review of FASD treatments that there appears to be promise in interventions that address specific clinical and neurodevelopmental deficits in children and those that focus on hyperactivity or arousal dysregulation. Unfortunately, as Paley and O’Connor (2009) indicated in their treatment review, by the time many children with
FASD are diagnosed in elementary school, the opportunity for early intervention has been missed. Of course, the key to early diagnosis and treatment provision throughout the childhood years and beyond is improved training for professionals who might be in a position to detect and/or diagnose FASD. Toward that end, four FASD Regional Training Centers have been established by the federal government to develop, implement, and evaluate new training programs and enhance current training programs for medical and allied health students and practitioners.

In the educational setting, the National Organization on Fetal Alcohol Syndrome (NOFAS) has provided a comprehensive school-based FASD Education and Prevention curriculum for grades K-12 which provides information about the effects of prenatal alcohol exposure on human development while simultaneously encouraging youth to be tolerant of all individuals, regardless of individual capabilities or disabilities. Missing in such efforts, however, is specific training in FASD for teachers involving screening and appropriate referral.

In summary, while the above research is preliminary, results suggest that interventions can make a difference in domains known to be deficient in FASD. As is evident from the initial success of these studies, the key to reducing secondary disabilities is a comprehensive approach to intervention that encompasses multiple systems of care, including neuropsychological assessment, case management, and interventions in multiple domains throughout the childhood years and beyond.

Dr. Natalie Novick Brown is a Licensed Psychologist in Washington and Florida with specialized training and expertise in the areas of developmental disabilities and fetal alcohol spectrum disorders (FASDs). She has practiced in both the clinical and forensic areas for 15 years and is certified in Washington State to conduct evaluations and risk assessments for the Division of Developmental Disabilities (DDD) and Department of Social and Health Services. As a Clinical Assistant Professor at the University of Washington, she consults with the Fetal Alcohol and Drug Unit regarding criminal behaviors in individuals with FASD diagnoses and other conditions involving developmental disability. Dr. Brown is the founder and Program Director/Chief Psychologist for FASD Experts, the only multidisciplinary FASD assessment group in the United States that operates in the forensic arena. For the past 3 years, she has also been testing and screening misdemeanor offenders suspected of having FASD who were referred by the Mental Health and Drug Courts in Seattle in order to determine their potential eligibility for coverage by the Division of Developmental Disabilities. Dr. Brown can be contacted by email at nknb@u.washington.edu.

References


Snyder, J., Manson, J., Stryde,R. and Block, G.W. (1997). Stimulants efficacy in children with FAS. In A. Streissguth & J. Kantor (Eds.), T

Streissguth & J. Kantor (Eds.), T


