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Case-control study of the association of use of health services by children with behavioural and developmental disorders with prenatal alcohol exposure

A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

for the degree

MASTER OF PUBLIC HEALTH
(Epidemiology/Biostatistics)

By

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FEBRUARY 2010
DECLARATION OF PLAGIARISM

I, Elizabeth Katwan, Student No. KTWELI001, declare that the work that I have submitted is my own and where the work of others has been used (whether quoted verbatim, paraphrased or referred to) it has been attributed and acknowledged.

Signature: ____________________________

Date: 1 - Feb - 2010
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ABSTRACT
Case-control study of the association of use of health services by children with behavioural and developmental disorders with prenatal alcohol exposure

Background
Prenatal alcohol exposure can result in a range of permanent birth defects known as Fetal Alcohol Spectrum Disorders (FASD). Fetal Alcohol Syndrome (FAS), which detrimentally affects the neurodevelopmental, physical, and social capabilities of children, is the most severe diagnosis on this scale of disorders. Research suggests that FASD rates exceed FAS in various populations. South Africa’s Western Cape region has one of the highest rates of FAS in the world.

Hypothesis
In populations where the prevalence of full-blown FAS is already known to be high, such as the Western Cape, other, less severe childhood developmental and behavioural disorders may be due to prenatal alcohol exposure.

Objectives
The aim of this research was to determine the odds of maternal alcohol use in children with behavioural and/or developmental disorders (BDD) in comparison to children free from behavioural disorders. This project also examined the average utilisation of health services by children with BDD as an arm of a larger study on the economic burden of FAS in South Africa.

Methods
Opportunistic sampling was employed to select parents or caretakers of 110 children aged 4 to 12 for interviews at a tertiary children’s public hospital in Cape Town. Health service utilization and maternal alcohol consumption habits were compared between 55 cases, children with BDD and 55 controls, children free from such disorders. Univariate analyses and logistic regression methods were used to determine these associations.

Ethics
The University of Cape Town Research Ethics Committee approved this study. Dr. T. Blake, Senior Medical Superintendent of Red Cross War Memorial Children’s Hospital granted access to Red Cross Hospital. Before each study interview was conducted, informed consent, which emphasized confidentiality of responses and the right to refuse to answer a question or withdraw from the interview, was taken from the adult respondent. We also explained to participants that they would remain anonymous and that their answers would not affect their child’s treatment in the clinics.

Results
BDD were significantly associated with current maternal alcohol consumption, maternal binge drinking in the last six months, and maternal alcohol use six months before pregnancy, but not significantly with reported maternal gestational drinking. The median number of visits to a clinic in the last six months was significantly higher for cases than for controls.

Conclusions
Childhood BDD among our study participants were not attributed to prenatal alcohol exposure. Current maternal alcohol consumption has a significant impact on BDD in children, possibly serving as a proxy for unstable home environments. The competing environmental factors that influence childhood BDD warrants further research.
SECTION I: Project Proposal

I. Introduction

Fetal Alcohol Syndrome (FAS) has been identified as a major health problem in the Western Cape, which indicates a need to prevent women from consuming alcohol during pregnancy. While past research has examined rates of FAS, it is necessary to investigate the full impact of prenatal alcohol exposure on alcohol related birth defects other than full-blown FAS. The research proposed here will help to estimate the full extent of the impact of alcohol consumption during pregnancy by determining the prevalence of reported prenatal alcohol exposure in children with behavioural and/or developmental disorders. Further this study will compare these children to a group of children free from such disorders with respect to the odds of maternal alcohol use and current health care utilisation.

A. Problem Identification

It is widely recognized that children born to women who drink alcohol while pregnant suffer from a wide array of social, physical, and neurodevelopmental disorders. These disorders carry life-long consequences for the mental health and social capabilities of the children. The extent of these problems can affect children’s abilities to socialize, benefit from education, and participate in the workforce. FAS is the most severe diagnosis from a range of problems known as Fetal Alcohol Spectrum Disorders (FASD). South Africa’s Western Cape region has one of the highest rates of FAS in the world (May and Gossage 2001), illustrating the pertinence of gestational period drinking as a major health problem. Further, research suggests that FASD rates exceed FAS in various populations (Thompson 1990, Sampson et al. 1997, May et al. 2006). Given the high prevalence of FAS, and the likely higher rates of FASD, plus the longevity of their associated problems, it is necessary to consider the extent of maternal drinking on various behavioural and developmental disorders, other than full-blown FAS. This will help to contribute to a better understanding of the scale of the impact of prenatal alcohol exposure in the Western Cape of South Africa.

B. Rationale and Motivation

Preventing women from consuming alcohol while pregnant or stopping women who consume alcohol from becoming pregnant, can avoid the manifestation in children of any of the outcomes within the spectrum of FASD. Since FASD is both preventable and very prevalent in South Africa, it is an important health problem around which to build interventions. To properly tackle this issue though, we must better understand the additional burden of maternal drinking on a wide variety of behavioural problems and developmental delays in children.

C. Literature Review

Prenatal alcohol exposure results in a spectrum of outcomes known as Fetal Alcohol Spectrum Disorders (FASD), which includes Fetal Alcohol Syndrome (FAS), partial FAS, Fetal alcohol effects, Alcohol-related neurodevelopmental disorder (ARND), and Alcohol-related birth defects (ARBD) (NIAAA 2006). While not a specific clinical diagnosis, FASD is an umbrella term that encompasses varying levels of “craniofacial malformations, neurological and motor deficits, intrauterine growth retardation, learning disabilities, and behavioral and social deficits” (NIAAA 2006) that arise from gestational alcohol exposure. The Institute of Medicine (1996) concluded that since

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1 This version of the proposal has been updated as per the recommendations of the UCT Ethics Committee approval letter (Appendix C). These changes were made under supervision of Professor Leslie London. Further changes in methodology are noted throughout the document.
most cases of prenatal alcohol exposure do not meet all of the criteria for a FAS diagnosis, the full extent of the impact of gestational period drinking is underestimated.

The severity of disabilities associated with gestational drinking is impacted by how much and how often alcohol is consumed, the term of pregnancy during which alcohol is consumed, and individual biological responses in both the mother and the infant (NIAAA 2006). Even low levels of alcohol exposure can lead to adverse behaviours in children (Sood et al. 2001), meaning that there really is no safe amount of alcohol that pregnant women can consume. It must be emphasized though that, if alcohol consumption is detected early enough in the pregnancy and stopped, the impact of alcohol on outcomes in infants can be reduced.

**FASD vs. FAS**

Early consideration of the ratio of FASD to FAS cases estimates the former diagnosis to be two to three times more common than the latter (Thompson 1990) and thus the consideration of less severe neurobehavioural conditions is important in fully estimating the impact of maternal alcohol consumption. Sampson et al. (1997) found FAS prevalence in the United States to be 0.33 to 2.00 per 1,000 births, but when factoring in alcohol related neurodevelopmental disorders (ARND), the estimates increased to 9.0 per 1,000 births.

More recently, May et al. (2006) measured rates of FAS and FASD in a region of Italy, finding even more jarring results. FAS prevalence rates were reported to be 3.7 to 4.7 per 1,000 children, while FASD ranged from 20.3 to 40.5 per 1,000 children. Considering FAS rates in rural areas of the Western Cape have been estimated to be 40.5 to 46.4 per 1,000 in children aged five to nine (May et al. 2000) and have been found to be on the rise at 65.2 to 74.2 per 1,000 children (Viljoen et al. 2005), the prevalence of other alcohol-related behavioural disorders could potentially be vast.

**Impact on Health Utilization**

Following this thinking, in terms of health service utilization FASD could pose a large additional burden. A study assessing differences in hospitalization between FAS cases, partial FAS cases, and controls (Kvigne et al. 2004), supports this possibility. They found an increased likelihood of ever having been hospitalized (OR=4.77; 95% CI: 1.75-13.37) as well as a significant difference in the total mean days being hospitalized between FASD children and controls (6.53 and 2.70 days respectively; p<0.001). The study further concluded that hospitalizations for the FASD children under study were likely underreported because these children were often placed with families outside of the health service area used (ibid).

**Diagnostic Tools for FASD**

One of the reasons that FASD cases are less often treated or recognized in the health services is the difficulty in diagnosing the disorder. There are several diagnostic tools available for use in diagnosing FASD (CDC 2004, IOM 1996, University of Washington 2004, Hoyme 2005). While the tools differ slightly, each with its own strengths and weaknesses, they are all based upon meeting varying levels of physical and neurobehavioural abnormalities as well as on gestational period alcohol consumption.

The Institute of Medicine (1996) provided one of the earliest templates of FASD diagnoses, which later guidelines have attempted to update and standardize. The Four-Digit Diagnostic Code (University of Washington 2004) breaks FASD diagnoses into four criteria: growth deficiency, FAS facial phenotype, central nervous system abnormalities, and prenatal alcohol exposure. The template of tools for diagnosing
FAS by the Centers for Disease Control (CDC) describe behavioural abnormalities which include cognitive deficits, motor functioning delays, attention problems, social skills problems, as well as other potential developmental discrepancies (2004). The Hoyme criteria (2005) differ from the aforementioned approaches because they require the alcohol consumption during pregnancy to be of excessive levels.

The majority of studies that compare FASD children to controls have focused on differences in central nervous system functioning, growth deficiency, and facial phenotypes. In this study though, we are focusing on whether the biological mother of children with behavioral and/or developmental disorders, other than FASD, drank during pregnancy. Determining prenatal alcohol exposure is the most difficult aspect of a FASD diagnosis to confirm, and yet is a crucial part of the diagnosis.

The CDC (2004) remarks that, due to the difficulties of confirming prenatal exposure to alcohol without documented evidence, such as in a retrospective study, suspected occurrence of maternal drinking should be reported as unknown. Prospective studies, such as one by Sood et al. (2001) in which blood alcohol levels of pregnant women were recorded throughout their gestational periods, are ideal for obtaining a true confirmation of prenatal alcohol exposure. Since laboratory-confirmed alcohol use is usually not possible, examining maternal drinking during past pregnancies must be based upon verbal reports.

There are several reasons why an accurate confirmation of maternal alcohol use is difficult in an historical approach. For many mothers it is difficult to admit to drinking during pregnancy because it is both stigmatized and they feel at fault for their child’s condition. Further some mothers may still drink heavily or have severe brain damage due to alcohol, making their reports unreliable. Another reason for the lack of information on prenatal alcohol exposure is that the caretakers of many FASD children are not their biological mothers (CDC 2004). These concerns have been based off of studies done in Western settings/First-World Nations, whereas it has been found (Croxford & Viljoen 1999) that women in South Africa more readily admit to drinking alcohol. For instance, in a recent study in the Northern Cape, 82% (p<0.001) of mothers of children with FAS or partial FAS that participated in the study admitted to drinking during pregnancy (Urban et al. 2008).

In a comparison of the various diagnostic tools for FASD, Astley (2006) concluded that without confirmation of gestational period drinking, final diagnoses of FAS cannot be made. Despite the difficulties in confirming prenatal alcohol exposure in the diagnosis of FASD, studying the drinking habits in a population, and especially among sexually active and/or pregnant women, is imperative to measuring the potential size of alcohol related disorders. This study does not intend to diagnose FASD cases, but purports that identifying cases of behavioural and/or developmental disorders and investigating the occurrence of prenatal alcohol exposure will help to estimate the extent of the impact of drinking during pregnancy.

**Alcohol Consumption Patterns**

Patterns of alcohol consumption in South Africa have been well studied (Parry et al. 2005, Schneider et al. 2007). Based on the 1998 South Africa Demographic and Health Survey, Parry et al. (2005) found drinking rates amongst women to be 17% and amongst men 45% and that one third of these current drinkers participated in risky level weekend drinking. Further, residents of urban areas consumed alcohol at higher rates that non-urban dwellers, a trend that remained in the 2003 South African Demographic and Health Survey (Department of Health & Medical Research Council 2007). This survey also concluded that the highest levels of South African female drinking occurs in the Northern Cape and Western Cape.
While these studies have measured drinking rates at a population level in South Africa, more specific work has been conducted to investigate the alcohol use amongst sexually active groups in Gauteng (Morojele et al. 2006), finding high correlation between drinking and unsafe sex. In light of the fact that much of the damage due to alcohol intake for a child occurs in the earliest stages of a pregnancy (Thompson 1990) and even highly educated women are relatively unaware of the consequences of prenatal alcohol exposure (Walker et al. 2005), these results could have detrimental consequences.

In a more direct link between alcohol use and its gestational period drinking, Croxford and Viljoen (1999) interviewed pregnant women in the Western Cape on their drinking habits during their current pregnancy as well as their knowledge about the effects of prenatal alcohol exposure on children. In the Cape Metropole region, 34.4% of the sampled women reported drinking during their index pregnancies. The rate of alcohol consumption during the gestational period amongst women in the Western Cape is slightly higher than estimates of drinking habits in other populations. For instance, a similar study in the United States, found the average prevalence of drinking in a group of pregnant women over four years to be 25%, with a decreasing trend in the practice; the first year rates ran as high as 32% and the final year rates were 20% (Serdula et al. 1991). In a retrospective study of alcohol use during pregnancy in Queensland, Australia (Rimmer & De Costa 2006), 24.6% of the study participants self-reported drinking during pregnancy. In a Toronto based study of binge drinking during pregnancy, as recorded in medical records, rates varied from 0.8% to 3.1% (Gladsone et al. 1997).

These two studies reflect how past and current research on gestational period drinking focuses on full-blown FAS outcomes, with less work regarding diagnoses of FASD and almost none on other less severe behavioural and/or developmental disorders, a gap that this work aims to fill. Expanding what is deemed an outcome of prenatal alcohol exposure to children with varying behavioural and developmental disorders, other than FAS, is an attempt to redefine the extent of the impact of gestational period drinking. Of further importance is the fact that all alcohol-related birth defects can be prevented; thus investigating the broad effects of prenatal alcohol exposure is an important contribution to public health in the Western Cape.

D. Aims and Objectives
The aim of this research is to determine the odds of prenatal alcohol exposure in children with behavioural and/or developmental disorders, other than FASD, in comparison to children free from such disorders. This project also aims to examine the average number of visits to health services by children with behavioural and/or developmental disorders as an arm of a larger study that aims to estimate the economic burden of FASD in South Africa.

Objectives:
1. To describe the population of 4 – 12 year old children with behavioural and/or developmental disorders seen at the Child and Family Unit of Red Cross Children’s Hospital during 2009.

2. To determine the prevalence of reported prenatal alcohol exposure in children with behavioural or developmental disorders compared to a population of controls who are free from such disorders attending the general Outpatient Department (OPD) of Red Cross Children’s Hospital.
III. Methods

This project will be conducted using a case control study design in which prenatal alcohol exposure will be retrospectively ascertained from both a population of children with behavioural and/or developmental disorders and a control population.

A. Population and sampling strategy

The health facilities from which cases and controls will be sampled have been purposively selected. Red Cross Children’s Hospital (RCH) is a referral hospital, where children are seen for various purposes and come from different areas of Cape Town. Within RCH, the general Outpatient Department has been selected for control selection. The Trauma unit may also need to be accessed to ensure that there are controls from the upper-end of the age range under study.¹

Vanguard CHC and Retreat CHC are accessed once a week by registrars from the Child and Family Unit (CFU) of RCH to cater to the needs of children with neurobehavioural disorders, thus rendering them reliable sources of confirmed cases.³ These registrars initially see the children at the Child and Family Unit, which is where their medical records are stored. A review of the medical records of case patients is necessary to exclude children with full-blown FAS, severe learning disorders, and known genetic disorders or teratogenic anomalies.

Table 1. Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>CASES</th>
<th>INCLUDED</th>
<th>EXCLUDED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children seen during 2009 at the Child &amp; Family Unit</td>
<td>FAS/FASD</td>
</tr>
<tr>
<td></td>
<td>Clinically recorded diagnosis of behavioural disorder, including:</td>
<td>Known genetic disorders or teratogenic anomalies</td>
</tr>
<tr>
<td></td>
<td>-Attention deficit disorder</td>
<td>Severe learning disorders</td>
</tr>
<tr>
<td></td>
<td>-Anxiety, stress disorder</td>
<td>Known to be HIV-positive</td>
</tr>
<tr>
<td></td>
<td>-Conduct problems</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Parent-child relationship problems</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Mild to marginal learning disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ages: 4-12</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CONTROLS</th>
<th>INCLUDED</th>
<th>EXCLUDED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children seen at Red Cross Children’s Hospital (General OPD) during duration of study in 2009</td>
<td>Same as above, plus:</td>
<td></td>
</tr>
<tr>
<td>Ages 4-12</td>
<td>Behavioural disorders as reported by parent/caretaker using our screening tool</td>
<td></td>
</tr>
</tbody>
</table>

Cases will be selected from Retreat CHC and Vanguard CHC³ in the following manner. During the aforementioned initial visit to RCH, all mothers of children with

¹ The Trauma Unit of RCH was not eventually accessed, because controls of all ages were recruited from the Outpatient Department.
³ After further consultation with the staff of the CFU, we decided against accessing patients at Retreat and Vanguard, instead recruiting patients seen by the CFU staff at weekly Developmental clinic, Behavioural clinic, Occupational Therapy (OT) and regular appointments on the CFU premises.
behavioural disorders who access Retreat and Vanguard and are eligible to participate in the study, will be approached to be interviewed. This method has been chosen so that the parents do not have to be called back to the facility to participate in the study. The registrars for Vanguard and Retreat see approximately four patients a week each at RCH for these preliminary visits (personal communication with Dr. Colleen Adnams). If this method does not yield enough case patients, the interviews will be done at Vanguard and Retreat CHCs before or after planned visits with the same registrars. Again, this will not require the parents to be called back to the facility specifically for this interview.

If these two methods still do not yield sufficient cases, a review of the medical records of children with behavioural disorders seen by the RCH registrars at Retreat and Vanguard in 2008 will be conducted. Systematic random sampling will be utilized starting from the most recent records in December 2008 and counting backwards every 6th file, until a sufficient sample size is achieved. The parents or caretakers, as proxy informants, of these case children will then be contacted and invited to participate in an interview at the clinics.

Controls will be selected through opportunistic sampling. The researcher/interviewer will be stationed in the waiting room of general OPD unit in RCH over a three-month period during various days and times. Since we want to see children of all ages specified in the inclusion criteria (4-12), we may need to select controls from the Trauma unit of RCH where there are more likely to be children in the older end of the spectrum (personal communication with Dr. Colleen Adnams). This interviewer/researcher will approach parents or caretakers that enter with a child to participate in the interview. Once they agree to participate and sign the informed consent, they will be asked three questions about the child’s behavior. If affirmative responses are given about the child for two of the three questions according to the parent or caretaker, the interview will be terminated at that point. These children will be excluded to ensure that the controls are free from any severe behavioural disorders.

Sample size
Sample size estimates have been calculated based upon two estimates of female drinking patterns. The 2003 South Africa Demographic and Health Survey found that 28.8% of women, aged 15 and up, in the Western Cape have consumed alcohol in the last twelve months (Department of Health & Medical Research Council 2007). More specifically, Croxford and Viljoen (1999) reported the rate of women attending antenatal clinics who drink during pregnancy in the Cape Metropole region to be 34.4%. Using these statistics as estimates of exposure in the control population, a desired power of 80%, and a 95% confidence level, several sample sizes were calculated with EpiCalc 2000 software (Table 4). Four hypothesized odds ratios between cases and controls and two ratios of cases to controls were examined to see what sample size would be most feasible and appropriate for this study.

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4 This recruitment strategy was not eventually necessary as we were able to recruit a sufficient number of case participants during the aforementioned weekly specialized clinics of the CFU.

5 Only the present adults with children aged 4-12 were approached from the Outpatient Unit; this was determined by the date of birth written on the outside of the medical folders.
Table 2. Sample size estimates

<table>
<thead>
<tr>
<th>Exposure in controls</th>
<th>Case to control ratio</th>
<th>OR=2.0</th>
<th>OR=3.0</th>
<th>OR=5.0</th>
<th>OR=10.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.8%</td>
<td>1:1</td>
<td>Cases=142 Controls=142 Total=284</td>
<td>Cases= 55 Controls=55 Total=110</td>
<td>Cases=25 Controls=25 Total=50</td>
<td>Cases=13 Controls=13 Total=26</td>
</tr>
<tr>
<td></td>
<td>1:2</td>
<td>Cases=106 Controls=213 Total=319</td>
<td>Cases= 41 Controls=82 Total=123</td>
<td>Cases=19 Controls=38 Total=57</td>
<td>Cases=10 Controls=20 Total=30</td>
</tr>
<tr>
<td>34.4%</td>
<td>1:1</td>
<td>Cases=134 Controls=134 Total=268</td>
<td>Cases= 53 Controls=53 Total=106</td>
<td>Cases=25 Controls=25 Total=50</td>
<td>Cases=14 Controls=14 Total=28</td>
</tr>
<tr>
<td></td>
<td>1:2</td>
<td>Cases= 101 Controls=202 Total=303</td>
<td>Cases= 40 Controls=80 Total=120</td>
<td>Cases=19 Controls=38 Total=57</td>
<td>Cases=10 Controls=20 Total=30</td>
</tr>
</tbody>
</table>

For this study a total sample size of 110 will be used, with a 1:1 case to control ratio, meaning 55 for each group. This was decided in light of the finding that the odds of having behavior problems and/or developmental delays were over ten times as likely among partial FAS cases when compared to controls (Kvigne et al. 2004). By using an odds ratio of 3.0 with the exposure rate among controls of 28.8% from the 2003 South Africa Demographic and Health Survey, the sample size of 110 will be larger than for what is necessary to detect a higher odds ratio, which will help to account for random error associated with the data collection. This sample size can also encompass the 34.4% exposure rate for controls found by Croxford and Viljoen (1999), which was specific to pregnant women, thus appropriate for this study.

B. Sampling Instruments

Information on prenatal alcohol exposure will be derived from interviews with the parents or current caretakers of the case and control populations. A questionnaire (Appendix B) has been created to capture data on a child’s age, gender, race, and behavioural habits as well as on the biological mother’s demographics and drinking history. While questions relating to alcohol use patterns and child behavior have been modified from previously validated measurement tools, this specific questionnaire will also be piloted for face validity and reliability amongst a representative population. The questionnaire will be translated into English, Xhosa, and Afrikaans versions to accommodate the participant’s language of choice.

Validity and Reliability of Sampling Instrument

The questionnaire contains closed and open-ended questions with four purposes: background information, drinking history and habits of the biological mothers, behavioural characteristics of the control children, and health service utilisation for the children. Questions related to drinking history and habits have been taken from existing tools that are repeatedly used in clinical practice, including the CAGE system, as well as questions from previous studies on alcohol use in the Western Cape (May et al. 2005, South African Demographic and Health Survey 1998). Confirming drinking history is a consistent challenge (Schorling 2005), and may prove further difficult as the caretakers of the case and control children may not be the biological mothers. Since a clinically confirmed blood alcohol level from the
gestational period is impossible to attain, an evaluation of prenatal alcohol exposure will be based upon self-report from the biological mother or a report of alcohol consumption from the knowledge of the current caretaker.

Questionnaire items related to behaviours of the children have been modified from the existing Four-Digit Diagnostic Code for FASD (University of Washington 2004); the purpose of these questions is to confirm that the controls, who will be opportunistically sampled, are free from behavioural disorders, and thus not cases. The participant will also answer questions regarding the utilisation of clinics/community health centres and hospitals on behalf of the children within the last six months. An interviewer will administer the questionnaire, making sure to phrase the questions according to whether the biological mother or another person is answering them. The researcher will train the interviewers in this process.

C. Limitations
This study has several potential sources of limitation. As in all case-control studies, recall bias is a potential problem. This bias is generally associated with cases having a better recollection of their exposure status than controls, but in the case of this study cases may actually under-report their exposure status due to the stigma surrounding alcohol consumption and FASD. A related concern is the possibility that the children’s biological mothers will not be accessible for interview and thus questions regarding them may lack total accuracy.

Selection bias may also limit the conclusions of the study in that opportunistic sampling is being used. While this sampling method has been chosen to reduce the burden of a study-specific clinic visit, it may bias the results toward people already utilising health services at a specific point in time. Since one of the objectives of the study though is to assess current health care utilisation, this bias will limit the study only in its comparability to the general population who does not access health services.

III. Budget
This study is being funded through a bursary from the National Research Foundation, Grant 443296. In addition to this budget for the project, the cost of coursework for one year and thesis fees for a Masters in Public Health from the University of Cape Town is being subsidized.

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
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<tr>
<td>Participant vouchers to Shoprite (R30 per participant x 120 participants)</td>
<td>R 3 600</td>
</tr>
<tr>
<td>Translation of forms (R 150 per hour x 8.5 hours)</td>
<td>R 1 275</td>
</tr>
<tr>
<td>Payment of interviewers (R 50 per hour x 121.5 hours)</td>
<td>R 6 075</td>
</tr>
<tr>
<td>Printing of informed consent and questionnaires (R 0.40 x 9 pages x 130 copies)</td>
<td>R 468</td>
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<td>TOTAL</td>
<td>R 11 418</td>
</tr>
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The budget was modified during the course of the study; changes throughout were reported to supervisors. The final budget is reported here.
IV. Timeline

<table>
<thead>
<tr>
<th>Month</th>
<th>Activities</th>
</tr>
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<tr>
<td>December 2008</td>
<td>Prepare protocol for ethics review</td>
</tr>
<tr>
<td></td>
<td>Research literature review</td>
</tr>
<tr>
<td>January 2009</td>
<td>Submission to UCT ethics review/necessary changes</td>
</tr>
<tr>
<td></td>
<td>Literature review</td>
</tr>
<tr>
<td>February-March 2009</td>
<td>Final changes for ethics approval if necessary</td>
</tr>
<tr>
<td></td>
<td>Submission to RCH for access approval</td>
</tr>
<tr>
<td>May-June 2009</td>
<td>Communication with staff of Child &amp; Family Unit and OPD of RCH</td>
</tr>
<tr>
<td></td>
<td>Recruitment of fieldworks</td>
</tr>
<tr>
<td>July-October 2009</td>
<td>Train interviewers; Pilot questionnaire</td>
</tr>
<tr>
<td></td>
<td>Data collection</td>
</tr>
<tr>
<td>November 2009</td>
<td>Data cleaning &amp; analysis</td>
</tr>
<tr>
<td></td>
<td>Write up results</td>
</tr>
<tr>
<td>December 2009-</td>
<td>Writing &amp; feedback</td>
</tr>
<tr>
<td>January 2010</td>
<td>Final changes under supervision</td>
</tr>
<tr>
<td></td>
<td>Submission to UCT</td>
</tr>
</tbody>
</table>

V. Ethics
This study, like all studies that retrieve information from human subjects, must uphold ethical standards regarding data collection, namely informed consent and confidentiality.

A. Informed consent
All participants will be required to provide signed informed consent (Appendix B) before being interviewed. The interviewer will describe the purpose of the study as well as what will be expected from the participant, including any potential risks. The right of study participants to decline or withdraw from the interview at any point as well as to refuse to answer any question should it cause any discomfort will be emphasized. The voluntary nature of the study will be stated so that no participant feels that he/she is being coerced into participation. The content for informed consent will be in accordance with guidelines issued by the Department of Health (2004) and the South African Medical Research Council (SAMRC 2001).

B. Language
Informed consent will be obtained in the language that the participant best understands. Consent forms will be available in Afrikaans, English, and Xhosa. Where literacy levels are of concern, the participant may choose to have the form read aloud. Interviews will be conducted in the language that the participant chooses as well.

C. Confidentiality and anonymity
The participant will be assured that any information provided during the interview will not be shared with anyone outside of the interviewer and/or the researcher. After the data is collected it will be kept in a file that only the researcher is able to access. Further, the information provided in the interview will not be traced back to the study participant. Instead participants will be coded with a number linked to their contact information, which will only be available to the researcher. After the data is collected, cleaned, and analyzed and the final version of the results has been written, the data will be destroyed.

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7 This timeline has been modified from the original proposal to reflect current progress.
8 All informed consent forms were read to the participants by the research team.
D. Beneficence
This study will not put the participants in any physical harm. The risks associated with the data collection are deemed minimal as it is interview based, but the interviewers will be trained in administration of the questionnaire and to be sensitive to the participants in the event that they feel any emotional discomfort. The interview questions may provoke feelings of anxiety, shame, and guilt due to the stigma associated with the subject matter.

While the results of this study do not directly benefit the participants, the public health implications of the study will help to target interventions related to alcohol use and abuse amongst pregnant and sexually active women. Further this project will contribute to a larger study estimating the economic burden of FASD in South Africa.

Each eligible participant will receive a voucher in the amount of R 30 to a local Shoprite grocery store. Further, participants who access the sites specifically for the interview will be reimbursed for the cost of transport to and from the interview.

VI. Dissemination strategy
The results of this study will be used as the partial completion of the requirements for a Masters in Public Health from the University of Cape Town. These results will also be reported back to the larger study on the economic costs of FASD to which it is contributing and to involved parties of the Child and Family Unit of RCH.

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9 No participants were required to come to the study sites specifically for participation in the study. Since the participants who were approached were already in the clinic at the time of the study, they were not reimbursed for transport.
VII. References


SECTION II: Literature Review

This literature review aims to summarize some of the research on alcohol related behavioural and developmental disorders and to highlight gaps in knowledge, including those that our study aims to fill. More specifically, the literature here provides background information on Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Spectrum Disorders (FASD), including diagnostic tools for the disorders and comparative prevalence rates. This review also examines alcohol consumption patterns among women. While some areas of research are rich with literature, such as defining and describing FAS, other areas, such as rates of behavioural and developmental disorders and health utilization data among South African children, are lacking. This study does not intend to examine FASD cases, but purports that investigating the occurrence of prenatal alcohol exposure in children with mild behavioural and/or developmental disorders will help to estimate the extent of the impact of drinking during pregnancy.

The search strategy for this review followed a pattern of learning, beginning with gaining a background of what FAS is, including symptoms, causes, and diagnostic tools. This led to research about FASD in terms of prevalence rates and severity in comparison to FAS. Research on alcohol consumption patterns among women was an important next step in understanding different approaches to collecting data on both current and prenatal alcohol use. Research done on FAS and alcohol use in South Africa helped to paint a population-specific picture of the extent of the problem locally and in comparison to worldwide rates. To ensure the time relevance of the literature review, works published before 1990 were excluded from this study. A second round of searching was done after the data was collected to update the review with more current work. Reviewing the literature topically helped to identify where this study fits and more importantly what it adds to the current body of knowledge.

What are FAS and FASD?
Prenatal alcohol exposure results in a spectrum of outcomes known as Fetal Alcohol Spectrum Disorders (FASD), which includes Fetal Alcohol Syndrome (FAS), partial FAS, Fetal Alcohol Effects, Alcohol-related Neurodevelopmental Disorder (ARND), and Alcohol-related birth defects (ARBD) (NIAAA 2006). While not a specific clinical diagnosis, FASD is an umbrella term that encompasses varying levels of “craniofacial malformations, neurological and motor deficits, intrauterine growth retardation, learning disabilities, and behavioral and social deficits” (NIAAA 2006) that arise from gestational alcohol exposure. The Institute of Medicine (1996) concluded that since most cases of prenatal alcohol exposure do not meet all of the criteria for a FAS diagnosis, the full extent of the impact of gestational period drinking is underestimated.

The severity of disabilities associated with gestational drinking is impacted by how much and how often alcohol is consumed, the term of pregnancy during which alcohol is consumed, and individual biological responses in both the mother and the infant (NIAAA 2006). Sood et al. (2001) conducted a prospective study on a cohort of pregnant women in 1986 and contacted them again six to seven years later in an attempt to establish a dose-response effect between levels of alcohol consumption and behavior disorders. While no direct dose-response was determined, the study found that even the lowest levels of alcohol exposure led to adverse behaviors in the children, meaning that there really is no safe amount of alcohol that pregnant women can consume. It must be emphasized though that, if alcohol consumption is detected
early enough in the pregnancy and stopped, the impact of alcohol on outcomes in infants can be reduced.

More recent work in the United Kingdom (Kelly et al. 2008) has found that low-level alcohol intake, 1-2 drinks per week, during pregnancy does not increase the likelihood of neurodevelopmental and behavioural disorders in children three years of age. As an observational study the conclusions of Kelly et al. (2008) have their own inherent limitations, and must also be considered in light of the findings from other studies on moderate levels of drinking. Jacobson & Jacobson (1999) found neurodevelopmental deficits among children whose mothers had consumed 7-14 drinks per week, considered a moderate level of alcohol consumption. The effect of maternal drinking was stronger if the mother had consumed several drinks at one time rather than a few drinks over several days, illustrating two points. First, as has been noted elsewhere (NASADAD 2005), the effect of binge drinking is notably predictive of neurological delays in children. Secondly, the patterns in which pregnant women drink have varying levels of impact (Larkby & Day 1997).

FASD vs. FAS
The variation in outcomes between FAS cases, partial FAS cases, and controls has been studied in several populations. One such study, on Northern Plains American Indians (Kvigne et al. 2004), compared the odds of five FASD diagnostic criteria, including prenatal alcohol exposure, amongst FAS children, incomplete FAS (those who met one to four of their criteria), and controls. Between the incomplete FAS cases and the controls, the odds ratios for several markers of central nervous system (CNS) dysfunction (Table 1) were found to be significant. The confidence intervals surrounding these odds ratios though, are very wide, showing a large degree of uncertainty within the study results.

Table 1. Statistically significant odds ratios for CNS dysfunction from Kvigne et al. 2004

<table>
<thead>
<tr>
<th>CNS dysfunction</th>
<th>FAS cases vs. Controls</th>
<th>Partial FAS cases vs. Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior problems</td>
<td>66.48 (17.64-277.79)</td>
<td>10.5 (3.21-34.31)</td>
</tr>
<tr>
<td>Developmental delays</td>
<td>122.1 (22.97-872.53)</td>
<td>14.0 (3.18-61.60)</td>
</tr>
<tr>
<td>Speech delays</td>
<td>37.38 (10.98-136.87)</td>
<td>14.5 (3.27-64.26)</td>
</tr>
<tr>
<td>Attention deficit disorder</td>
<td>8.5 (1.39-51.85)</td>
<td>21.0 (2.64-166.81)</td>
</tr>
<tr>
<td>Learning disabilities</td>
<td>9.0 (1.89-42.95)</td>
<td>14.0 (1.2-113.79)</td>
</tr>
</tbody>
</table>

The odds ratios for the occurrence of other categories of CNS dysfunction between FAS cases and controls were higher than those between partial FAS cases and controls within the study by Kvigne et al. (2004), showing that the symptoms of FAS can be more extreme than other FASD diagnoses. In terms of public health implications though, FASD has been found to be more prevalent at the population level. This means that the population-attributable risk due to prenatal alcohol exposure, or the reduction in incidence of an outcome that would be observed if the exposure was removed (Joubert 2007), is larger for FASD cases than for full-blown FAS.

Early consideration of the ratio of FASD to FAS cases estimates the former diagnosis to be two to three times more common than the latter (Thompson 1990) and thus the consideration of less severe neurobehavioural conditions is important in fully estimating the impact of maternal alcohol consumption. Sampson et al. (1997) found FAS prevalence in the United States to be 0.33 to 2.00 per 1,000 births, but when factoring in alcohol related neurodevelopmental disorders (ARND), the estimates
increased to 9.0 per 1,000 births. More recently, May et al. (2006) measured rates of FAS and FASD in a region of Italy, finding even more jarring results. FAS prevalence rates were reported to be 3.7 to 4.7 per 1,000 children, while FASD ranged from 20.3 to 40.5 per 1,000 children. Considering FAS rates in rural areas of the Western Cape have been estimated to be 40.5 to 46.4 per 1,000 in children aged five to nine (May et al. 2000) and have been found to be on the rise at 65.2 to 74.2 per 1,000 children (Viljoen et al. 2005), the prevalence of other alcohol-related behavioural disorders could potentially be vast.

Following this thinking, in terms of health service utilization FASD could pose a large additional burden. The study by Kvigne et al. (2004) assessed differences in hospitalization between FAS cases, partial FAS cases, and controls, supports this possibility. They found an increased likelihood of ever having been hospitalized (OR=4.77; 95% CI: 1.75-13.37) as well as a significant difference in the total mean days being hospitalized between FASD children and controls (6.53 and 2.70 days respectively; p<0.001). The study further concluded that the hospitalizations for the FASD children under study were likely underreported because these children were often placed with families outside of the health service area used (ibid).

Another inquiry into the difference in service utilization for FASD cases was a pilot study comparing mental health provision amongst these children versus a population of attention-deficit/hyperactivity disorder (ADHD) children (Mills, McLennan & Caza 2006). Through self-report and mailed questionnaires directed at caregivers of children under age seven within two specialized facilities during 2000 and 2002, it was found that FASD children had significant variation in the combination of types of care received, but over 50% of FASD cases visited one or more of the health care professionals listed in Table 2.

<table>
<thead>
<tr>
<th>Health Professional</th>
<th>FASD (n=14)</th>
<th>ADHD (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family doctor</td>
<td>78.6%</td>
<td>86.7%</td>
</tr>
<tr>
<td>Speech and language pathologist</td>
<td>78.6%</td>
<td>80.0%</td>
</tr>
<tr>
<td>Occupational therapist</td>
<td>71.4%</td>
<td>60.0%</td>
</tr>
<tr>
<td>Pediatrician</td>
<td>64.3%</td>
<td>46.7%</td>
</tr>
<tr>
<td>Psychiatrist</td>
<td>57.1%</td>
<td>80.0%</td>
</tr>
<tr>
<td>Mental health or Behaviour therapist</td>
<td>50.0%</td>
<td>60.0%</td>
</tr>
<tr>
<td>Psychologist</td>
<td>35.7%</td>
<td>46.7%</td>
</tr>
<tr>
<td>Any mental health professional</td>
<td>64.3%</td>
<td>86.7%</td>
</tr>
</tbody>
</table>

Since this is only a small pilot study, which limits its statistical power, the overall conclusions were that in general, FASD children are less often referred to mental health professionals by their primary physicians than ADHD children and have a different point of entry into the health system. In light of recent research, which found that FASD is still mistaken for ADHD (Greenbaum et al. 2009), more work like this pilot study will help to tease out differences between FASD and other behavioural disorders.

**Diagnostic Tools for FASD**

One of the reasons that FASD cases are less often treated or recorded in the health services is that since it is not a specific clinical diagnosis, it is difficult to precisely recognize. In addition, confirming maternal drinking habits during the index pregnancy is the most elusive component in the diagnosis.
There are several diagnostic tools available for use in diagnosing FASD, including ones from the Centers for Disease Control (CDC 2004), Institute of Medicine (IOM 1996), the Four-Digit Diagnostic Code (University of Washington 2004), and the Hoyme criteria (2005). While the tools differ slightly, each with its own strengths and weaknesses, they are all based upon meeting varying levels of physical and neurobehavioural abnormalities as well as on gestational period alcohol consumption. The Institute of Medicine (1996) provided one of the earliest templates of FASD diagnoses, upon which these later guidelines have attempted to update and standardize.

The Four-Digit Diagnostic Code (University of Washington 2004) breaks FASD diagnoses into four criteria: growth deficiency, FAS facial phenotype, central nervous system abnormalities, and prenatal alcohol exposure. Each potential case of FAS is assigned a score off an ordinal scale within each category, which forms the basis for placement in one of twenty-two categories of FASD. The multitude of categories under FASD illustrates both the difficulty of diagnosis as well as the breadth of impact of prenatal alcohol exposure.

While the two most severe classifications from the Four-Digit code pertain to FAS, the twenty remaining categories demonstrate how wide the range of damage associated with prenatal alcohol exposure is. The effect of prenatal alcohol exposure on development varies beyond timing and quantity of consumption. Genetic factors, educational attainment of the parents, maternal age, and environmental factors contribute to the variance in effect (Kalberg & Buckley 2006).

The Centers for Disease Control (2004) also provide a template of tools for diagnosing FAS. For behavioural abnormalities, their guidelines include cognitive deficits, functioning deficits, motor functioning delays, attention problems, social skills problems, as well as other potential developmental discrepancies. The guidelines proclaim a deficit in three or more specific areas for a child’s age group sufficient to diagnose FAS. The Hoyme criteria (2005) differ from the aforementioned approaches because they require the alcohol consumption during pregnancy to be of excessive levels.

The majority of studies that compare FASD children to controls have focused on differences in CNS functioning, growth deficiency, and facial phenotypes, but determining whether a child’s biological mother drank during pregnancy, a crucial part of the diagnosis, is less common due to how difficult it is to confirm. The CDC (2004) remarks that, due to the difficulties of confirming prenatal exposure to alcohol without documented evidence, such as in a retrospective study, suspected occurrence of maternal drinking should be reported as unknown. Prospective studies, such as one by Sood et al. (2001) in which blood alcohol levels of pregnant women were recorded throughout their gestational periods, are ideal for obtaining a true confirmation of prenatal alcohol exposure. Since laboratory-confirmed alcohol use is usually not possible, examining maternal drinking during past pregnancies must be based upon verbal reports.

There are several reasons why an accurate confirmation of maternal alcohol use is difficult in an historical approach. For many mothers it is difficult to admit to drinking during pregnancy because it is both stigmatized and they feel at fault for their child’s condition. Further some mothers may still drink heavily or have severe brain damage due to alcohol, making their reports unreliable. Another reason for the lack of information on prenatal alcohol exposure is that the caretakers of many FASD children are not their biological mothers (CDC 2004). These concerns have been
based off of studies done in Western settings/First-World Nations, whereas it has been found (Croxford & Viljoen 1999) that women in South Africa more readily admit to drinking alcohol. For instance, in a recent study (Urban et al. 2008) in the Northern Cape, 82% (p<0.001) of mothers of children with FAS or partial FAS that participated in the study admitted to drinking during pregnancy.

In a comparison of the various diagnostic tools for FASD, Astley (2006) concluded that without confirmation of gestational period drinking, a final diagnosis of FAS cannot be made. Despite the difficulties in confirming prenatal alcohol exposure in the diagnosis of FASD, studying the drinking habits in a population, and especially among sexually active and/or pregnant women, is imperative to measuring the potential size of alcohol related disorders.

**Alcohol Consumption Patterns**

Patterns of alcohol consumption in South Africa have been well studied (Parry et al. 2005, Schneider et al. 2007). Based on the 1998 South Africa Demographic and Health Survey, Parry et al. (2005) found drinking rates amongst women to be 17% and amongst men 45% and that one third of these current drinkers participated in risky level weekend drinking. Further, residents of urban areas consumed alcohol at higher rates than non-urban dwellers, a trend that remained in the 2003 South African Demographic and Health Survey (Department of Health & Medical Research Council 2007). This survey also concluded that the highest levels of South African female drinking occur in the Northern Cape and Western Cape. The impact of high drinking rates has more recently been studied in terms the contribution of alcohol to the burden of disease for 2000 in South Africa (Schneider et al. 2007). The burden of disease due to alcohol consumption in 2000 accounted for 7.1% of all deaths and 7.0% of disability-adjusted life years.

While these studies have measured drinking rates at a population level in South Africa, more specific work has been conducted to investigate the alcohol use amongst sexually active groups (Morojele et al. 2006) as well as amongst pregnant women (Croxford & Viljoen 1999). In a study conducted to estimate the association between alcohol and risky sexual behaviour, Morojele et al. (2006) found a high correlation between drinking and unsafe sex in Gauteng province. The impact of the link between these two factors has important consequences for estimating the potential effect of women who drink on developmental and behavioural outcomes in children. Further, since much of the damage due to alcohol intake for a child occurs in the earliest stages of a pregnancy (Thompson 1990) and even highly educated women are relatively unaware of the consequences of prenatal alcohol exposure (Walker et al. 2005) this observational study in Gauteng, which helps to identify women who drink, could be used to promote safe sexual practices among them as a FASD prevention strategy.

In a more direct link between alcohol use and its gestational period drinking, Croxford and Viljoen (1999) interviewed pregnant women in the Western Cape on their drinking habits during their current pregnancy as well as their knowledge about the effects of prenatal alcohol exposure on children. In the Cape Metropole region, 34.4% of the sampled women reported drinking during their index pregnancies. They further noted that women who consumed alcohol while pregnant were actually more knowledgeable about the harmful effects of gestational period drinking than their non-drinking counterparts. While the reason for this seemingly counterintuitive finding, was not reported, one can speculate that a health care professional could have educated women that they suspected were drinking during pregnancy on the consequences of this action. As noted in a study on alcohol use after pregnancy was
discovered (O’Connor & Whaley 2006), knowledge about the effects of prenatal alcohol exposure is not necessarily sufficient to alter behavior.

The rate of alcohol consumption during the gestational period amongst women in the Western Cape is slightly higher than estimates of drinking habits in other populations. For instance, a similar study in the United States, found the average prevalence of drinking in a group of pregnant women over four years to be 25%, with a decreasing trend in the practice; the first year rates ran as high as 32% and the final year rates were 20% (Serdula et al. 1991). In a retrospective study of alcohol use during pregnancy in Queensland, Australia (Rimmer & De Costa 2006), 24.6% of the study participants self-reported drinking during pregnancy. In a Toronto based study of binge drinking during pregnancy, as recorded in medical records, rates varied from 0.8% to 3.1% (Gladstone et al. 1997).

Mothers of full-blown FAS children in the Western Cape have been studied in a retrospective manner to examine their characteristics and potential risk factors (Viljoen et al. 2002, May et al. 2005). These studies examined the association between alcohol consumption and FAS from a different perspective by analyzing differences between the mothers of FAS cases and control children to determine risks for the development of the disorder. Major findings from this work were that many mothers of FAS children were raised in homes where alcohol was regularly consumed, showing a possible trend towards multi-generational FAS incidence. Interestingly both studies found that mothers of cases and controls were not vastly different in demographic characteristics and some drinking patterns. May et al. (2005) found that 20% of control mothers drank during pregnancy; whether their children were totally free from any of the neurobehavioural disorders was not specified.

Research Gaps and Needs
The works described in this review reflect how past and current research on gestational period drinking focuses on full-blown FAS outcomes, with less work towards less severe diagnoses, a gap that this study aims to fill. Expanding what is deemed an outcome of prenatal alcohol exposure to children with varying behavioural and/or developmental disorders, other than FASD, is an attempt to redefine the extent of impact of gestational period drinking. This type of research is imperative in the Western Cape, since FAS is already known to be highly prevalent and thus rates of less severe alcohol-attributed behavioural disorders are potentially vast.

Other areas of research that would contribute to a better understanding of an association between prenatal alcohol exposure and mild behavioural/developmental disorders would be to find patterns for varying effects of alcohol use in pregnancy. Two examples of this would be to establish a dose-response gradient for alcohol use and severity of diagnosis or to gain more knowledge on the effect of timing of alcohol use. Unfortunately, experimental trials to accurately measure prenatal alcohol use would not be ethically sound.

A major goal for research on alcohol-attributed disorders would be to increase professional knowledge surrounding the less severe end of the FASD continuum. In cases where health professionals have poor knowledge of FASD (Gray et al. 2009), it is likely because unlike full-blown FAS, FASD is not a specific clinical diagnosis. This can lead to underreporting of less severe alcohol-attributed developmental disorders because it is confused for other behavioural disorders, such as ADHD (Greenbaum et al. 2009). Another consequence of poor knowledge surrounding FASD by health
professionals is the detrimental toll it takes on preventing further cases of alcohol related birth defects. A study in the United States found that while most doctors do counsel about the effects of gestational drinking, they do not do so with all of their patients (O’Connor & Whaley 2006). A basic understanding that prenatal alcohol exposure can result in a wide array of developmental and behavioural disorders must be universal in prenatal care.

Another area of research that needs attention is the effect of current maternal alcohol use on the behaviors and development of children. While this correlation does not follow a biological pathway, it could help to redefine the impact of maternal alcohol use beyond the gestational era, through social pathways. May et al. (2005) asked questions about current alcohol use among parents of FAS children in South Africa but did not propose any mechanisms for the associations they explored. This study hopes to gain further insight into the association between current maternal drinking and behavioral/developmental disorders in children.

Finally, there is paucity in research on health utilization rates and prevalence of childhood behavioral/developmental disorders in South Africa. In terms of utilization, there is limited data on primary health care access rates from District Health Information Systems (2006) estimates, but this does not provide information about tertiary care, including specialized mental health provision. Further, without normative data on health utilization in children, there is little against which to compare research on health usage among children with behavioural/developmental delays. While health utilization was not the primary focus of this study, simple questions regarding access were asked to form a comparison between children with behavioural/developmental disorders and control children.

In addition, the reported prevalence of behavioural/developmental disorders among South African children is scarce. For future research on alcohol-attributed disorders, having such rates would help to contextualize the broad effects of prenatal alcohol exposure, an important health contribution to the Western Cape.
References


SECTION III: Journal Article

Title Page

Childhood behavioral and developmental disorders: association with maternal alcohol consumption and use of health services in Cape Town, South Africa
Prenatal alcohol exposure can result in a range of permanent birth defects known as Fetal Alcohol Spectrum Disorders (FASD). Fetal Alcohol Syndrome (FAS), which detrimentally affects the neurodevelopmental, physical, and social capabilities of children, is the most severe diagnosis on this scale of disorders. Diagnoses of FASD are most accurately made between the ages of 3 and 10 years. The various tools for diagnosing FASD differ slightly, but are all based upon meeting varying levels of growth deficiency, FAS facial phenotype, central nervous system abnormalities, including behavior problems, developmental and speech delays, attention deficit disorder, and learning disabilities, and prenatal alcohol exposure.

The number of tools for detecting FASD and the varying levels and components of the diagnosis, the most elusive of which is confirming prenatal alcohol exposure, hint at the difficulty of diagnosis. Recently, Greenbaum et al. found that FASD is still often misdiagnosed as attention-deficit hyperactivity disorder (ADHD). It is thus likely that among children with behavioral and/or developmental disorders (BDD) other than FASD, there are children who were exposed to gestational period alcohol consumption and either did not meet all of the diagnostic criteria for FASD or have FASD but have not been diagnosed. What this means is that the full impact of gestational period drinking on birth defects in children is underestimated. In populations where the prevalence of full-blown FAS is already known to be high,
there is a possibility that other, less severe childhood developmental and behavioral disorders may be due to prenatal alcohol exposure.

South Africa’s Western Cape Province has one of the highest rates of FAS in the world. Additionally, FASD rates exceed FAS in various populations. Given the high prevalence of FAS in rural areas of the Western Cape, 65.2 to 74.2 per 1,000 children, plus the longevity of their associated problems, it is necessary to investigate the additional burden of gestational maternal drinking on a wide variety of adolescent behavioral problems and developmental delays, other than FAS. Research into the prevalence of behavioral and developmental types of disorders in South Africa is scarce, specifically regarding childhood behavioural disorders. However small-scale studies in rural areas report rates of mild intellectual disability in children aged two to nine to be 29.1 per 1,000 and rates of mild learning disabilities in children under ten years to be 17.1 per 1,000.

Patterns of alcohol consumption in South Africa have been well studied. The 2003 South African Demographic and Health Survey concluded that the highest levels of female drinking occur in the Northern Cape and Western Cape provinces. More specific work has been conducted to investigate alcohol use among sexually active groups as well as among pregnant women in South Africa. Retrospective studies on prenatal alcohol exposure have also been conducted among mothers of FAS children in South Africa, but there has been little research on the association between gestational period drinking and less severe forms of FASD presenting as BDD. Additionally, as hinted in other studies on developmental health of South African children, the impact of home environment, such as current maternal drinking, on children’s behavior and consequent healthcare needs, needs attention.

The health care utilization patterns of children with BDD in South Africa are unknown. In 2006, estimates for general primary health care (PHC) utilization from the National Department of Health for the average number of visits to a PHC facility per year in the Western Cape were 4.9 and 2.6 for children under five years and children five and above, respectively. While little data have been collected on health utilization among behaviorally and/or developmentally disordered children in South Africa, one can project that since FASD children are more likely to have been hospitalized than controls that children with other, less severe diagnoses may also pose an additional burden on health service utilization.

METHODS

Population, Sampling, and Design
This study was conducted using a case control design in which maternal alcohol consumption and child health utilization was ascertained from the parents or caretakers of a population of 55 children aged 4-12 with behavioral and/or developmental disorders and 55 control children without BDD in the same age range. The sample size of 110 participants was based on a 1:1 case to control ratio, an anticipated odds ratio of 3.0, statistical power of 0.8, an \( \alpha \) of 0.05, an anticipated prevalence of alcohol consumption among controls of 28.8% from data on alcohol use among South African women, and feasibility of the study.

Opportunistic sampling was used to recruit both cases and controls. Cases, children with various BDD, were sampled from Developmental Clinic, Occupational Therapy Clinic, and Behavioral Clinic, or from the Child and Family Unit (CFU) linked to the Red Cross War Memorial Children’s Hospital (RCH), a tertiary care public hospital in
Cape Town, South Africa. These clinics see children who have been referred through health services or schools. Control children were recruited from the general Outpatient Department (OPD) of the same hospital. Adults presenting with the index child were interviewed and given a grocery voucher as compensation for their participation after the interview.

Table 1. Inclusion and Exclusion Criteria for Participation

<table>
<thead>
<tr>
<th>INCLUDED</th>
<th>EXCLUDED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CASES</strong></td>
<td>Children seen during 2009 at the CFU, Developmental Clinic, Occupational Therapy Clinic, or Behavioral Clinic</td>
</tr>
<tr>
<td></td>
<td>Clinically recorded diagnosis of behavioural disorder, including:</td>
</tr>
<tr>
<td></td>
<td>- Attention deficit hyperactivity disorder</td>
</tr>
<tr>
<td></td>
<td>- Anxiety, stress disorder</td>
</tr>
<tr>
<td></td>
<td>- Conduct problems</td>
</tr>
<tr>
<td></td>
<td>- Parent-child relationship problems</td>
</tr>
<tr>
<td></td>
<td>- Mild to marginal learning disorders</td>
</tr>
<tr>
<td>Ages: 4-12</td>
<td></td>
</tr>
<tr>
<td><strong>CONTROLS</strong></td>
<td>Children seen in OPD of RCH during duration of study in 2009</td>
</tr>
<tr>
<td>Ages: 4-12</td>
<td></td>
</tr>
</tbody>
</table>

CFU=Red Cross Child and Family Unit; OPD=Outpatient Department; RCH= Red Cross War Memorial Children’s Hospital

Clinic records were reviewed during already scheduled appointments to identify cases that met the study inclusion criteria (Table 1). Parents or caretakers present with these cases were then recruited. When necessary, clinic staff determined patient eligibility at the end of consultation and, if the patient’s caregiver was willing, referred them to the research team.

Adults caregivers of control children who met the inclusion criteria (Table 1) were asked to participate in a research study while they waited to see a doctor. Screening questions, which spoke to the child’s ability to pay attention, ease of fitting into new social situations and age appropriateness of his/her behavior and which were based on the existing Four-Digit Diagnostic Code for FASD were used to exclude potential controls with behavioral or developmental difficulties.

Parents or caregivers of the children were interviewed in their first language. The questionnaire consisted of closed and open-ended questions in four domains: basic background information, including respondent-child relationship; child health service utilization questions; maternal alcohol consumption habits; and screening questions regarding the child’s behavior and social skills, for controls only.

Questions related to alcohol consumption were taken from previous studies on alcohol use in the Western Cape and included the CAGE screening tool for alcohol abuse. A score of two or more, out of four, is considered problem drinking on the CAGE scale. The question regarding binge drinking used a definition of five or more drinks on one occasion to be a binge. The questionnaire was structured in a specific order, following methods that have been shown to reduce respondent
resistance and improve recall of past events.\textsuperscript{19,20} It began with non-confrontational background and child health utilization questions, followed by inquiries into current drinking habits of the mother to which the final questions about drinking before and during the time of pregnancy were compared.

Before the interviews were conducted, informed consent, which emphasized confidentiality of responses and the right to refuse to answer a question or withdraw from the interview, was taken from the adult respondent. We also explained that participation was voluntary and anonymous and that answers would not affect the children’s treatment in the clinics.

**Statistical Analysis**

The data was explored, using STATA10 software,\textsuperscript{26} for possible patterns in the distributions of cases and controls using Chi-squared tests for categorical data and Wilcoxon rank-sum tests for non-parametric continuous data. Unconditional multivariate logistic regression, estimating odds ratios (OR) and 95% confidence intervals (CI), was used to explore the relationship between alcohol consumption variables and an outcome of BDD, controlling for potential confounders such as the use of a proxy respondent (versus the biological mother) and the age of the child (Model 1) and additionally including, the gender of the child (Model 2).

**RESULTS**

**Background information**

The response rate amongst eligible cases was 100%. Ten potential control children of the 72 total controls (13.9%) that were approached were excluded through the screening questions. Seven potential controls turned the researcher down when asked to participate in an interview, resulting in a response rate of 88.7% (55/62) amongst eligible controls. The median ages of case and control children (8 and 7 respectively) and of the ages of their mothers during pregnancy (27 and 26 respectively) were not significantly different (Table 2). Case children were more likely to be male than control children (74.5% versus 45.5%; \(p=0.002\)) and less likely to be accompanied by a biological mother (72.7% versus 92.7%; \(p=0.006\)).

**Maternal Alcohol Consumption**

More than half of the mothers had ever consumed alcohol (56.4%), but there was no significant difference between cases and controls in ever having drunk alcohol (58.2% versus 54.5%; \(p=0.70\)). Most mothers were not currently drinking (78.2%) at the time of the interview. Frequencies of current drinking were significantly higher amongst mothers of cases than mothers of controls (30.9% versus 12.7%; \(p=0.02\)). The majority of mothers (75.4%) were not considered problem drinkers, having CAGE scores less than two. There was no significant difference (\(p=0.54\)) in the prevalence of problem drinking according to CAGE scores of mothers of cases and controls (Table 2).

Most women (64.5%) reported they did not drink in the six months before they were pregnant with the child of interest. Among the case mothers, the frequency of drinking six months before pregnancy was higher than this frequency among control mothers (40.0% versus 21.8%; \(p=0.04\)). The majority of mothers reported not drinking during pregnancy (81.8%); two respondents did not know whether the biological mother drank during pregnancy. The frequency of gestational drinking was lower among control mothers than among case mothers but was not significantly different (12.7% versus 20.0%; \(p=0.263\)).
Table 2. Demographic and Alcohol Consumption Characteristics of Study Participants, Cape Town, South Africa, 2009

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Pop.</th>
<th>Cases</th>
<th>Controls</th>
<th>Difference a (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of child</strong></td>
<td>Median Values</td>
<td>7 years (IQR: 5-10)</td>
<td>8 years (IQR: 6-10)</td>
<td>7 years (IQR: 5-10)</td>
</tr>
<tr>
<td><strong>Age of mother during pregnancy</strong></td>
<td>Median Values</td>
<td>26 years (IQR: 22-31)</td>
<td>27 years (IQR: 22-31)</td>
<td>26 years (IQR: 22-31)</td>
</tr>
<tr>
<td><strong>Gender of child</strong></td>
<td>Female (Ref.)</td>
<td>44 (40.0%)</td>
<td>14 (25.5%)</td>
<td>30 (54.5%)</td>
</tr>
<tr>
<td><strong>Respondent</strong></td>
<td>Proxy (Ref.)</td>
<td>19 (17.3%)</td>
<td>15 (27.3%)</td>
<td>4 (7.3%)</td>
</tr>
<tr>
<td><strong>Mother has ever consumed alcohol</strong></td>
<td>No (Ref.)</td>
<td>48 (43.6%)</td>
<td>23 (41.8%)</td>
<td>25 (45.5%)</td>
</tr>
<tr>
<td><strong>Mother drinks alcohol now</strong></td>
<td>Yes</td>
<td>62 (56.4%)</td>
<td>32 (58.2%)</td>
<td>30 (54.5%)</td>
</tr>
<tr>
<td><strong>Mother binged in last 6 months</strong></td>
<td>No (Ref.)</td>
<td>86 (78.2%)</td>
<td>36 (69.1%)</td>
<td>48 (87.3%)</td>
</tr>
<tr>
<td><strong>CAGE score</strong></td>
<td>0-1 (Ref.)</td>
<td>93 (84.5%)</td>
<td>42 (76.4%)</td>
<td>51 (92.7%)</td>
</tr>
<tr>
<td></td>
<td>≥ 2</td>
<td>83 (75.4%)</td>
<td>39 (70.9%)</td>
<td>44 (80.0%)</td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td>24 (21.8%)</td>
<td>13 (23.6%)</td>
<td>11 (20.0%)</td>
</tr>
<tr>
<td></td>
<td>0 (0.0%)</td>
<td>3 (2.7%)</td>
<td>3 (5.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Mother drank 6 months before pregnancy</strong></td>
<td>No (Ref.)</td>
<td>34 (30.9%)</td>
<td>22 (40.0%)</td>
<td>12 (21.8%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>3 (2.7%)</td>
<td>1 (1.8%)</td>
<td>2 (3.6%)</td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td>2 (1.8%)</td>
<td>1 (1.8%)</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td><strong>Mother drank during pregnancy</strong></td>
<td>No (Ref.)</td>
<td>90 (81.8%)</td>
<td>42 (76.4%)</td>
<td>48 (87.3%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>18 (16.4%)</td>
<td>11 (20.0%)</td>
<td>7 (12.7%)</td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td>2 (1.8%)</td>
<td>2 (3.6%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

IQR=interquartile range

a The Wilcoxon rank-sum test was used for non-parametric continuous data and the Chi-squared test was used for categorical data.

b Binge drinking was considered having five or more drinks on one occasion.

c CAGE is a four-question screening tool for alcohol abuse. A score of 2 or above is considered problem drinking.

The odds of the mother having consumed alcohol in the six months prior to the pregnancy of interest among cases was 2.17 (95% CI=0.90, 5.28) times that of controls, controlling for use of a proxy respondent and the age of the child and 3.00 (95% CI=1.12, 8.03) times that of controls, additionally controlling for gender of the child (Table 3). The likelihood of alcohol consumption during pregnancy, controlling for use of a proxy respondent and the age of the child, was not significantly higher among cases than controls (OR=1.53; 95% CI=0.52, 4.51) nor was it significant when additionally controlling for the child’s gender (OR=1.77; 95% CI=0.57, 5.53).

Children with behavioral and/or developmental disorders were approximately three times more likely than children without BDD to have a mother who currently drinks alcohol (OR=2.94; 95% CI=1.06, 8.12) controlling for use of a proxy respondent and the age of the child and similarly when additionally adjusting for the child’s gender.
Similarily, children with BDD were over four times more likely than control children to have a mother who binged on alcohol in the last six months (OR=4.40; 95% CI=1.10, 17.64) controlling for use of a proxy respondent and the age of the child and higher yet when additionally adjusting for the child’s gender (OR=4.67; 95% CI=1.10, 19.90).

Table 3. Crude and Adjusted Odds Ratios for the Association Between Maternal Alcohol Consumption and Childhood Behavioral and/or Developmental Disorders in a Sample Population, Cape Town, South Africa, 2009

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR Model 1 a (95% CI)</th>
<th>Adjusted OR Model 2 b (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Era Alcohol Consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drank 6 months before pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (Ref.)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>2.37 (1.02, 5.51)</td>
<td>2.17 (0.90, 5.28)</td>
<td>3.00 (1.12, 8.03)</td>
</tr>
<tr>
<td>Drank during pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (Ref.)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.80 (0.64, 5.05)</td>
<td>1.53 (0.52, 4.51)</td>
<td>1.77 (0.57, 5.53)</td>
</tr>
<tr>
<td>Current Alcohol Consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother drinks alcohol now</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (Ref.)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>3.07 (1.15-8.15)</td>
<td>2.94 (1.06, 8.12)</td>
<td>2.98 (1.02, 8.70)</td>
</tr>
<tr>
<td>Mother binged in last 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (Ref.)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>4.86 (1.29-18.35)</td>
<td>4.40 (1.10, 17.64)</td>
<td>4.67 (1.10, 19.90)</td>
</tr>
</tbody>
</table>

OR=Odds Ratio; CI=Confidence interval
a Adjusted for use of a proxy respondent and age of child
b Adjusted for use of a proxy respondent, age of child, and gender of child

Health Utilization
Case children visited outpatient clinics significantly more times in the last six months than control children (median 6 versus 2; p<0.001). There was no difference in the number of hospitalizations in the last six months. Of the 110 total participants, only 23 (13 controls and 10 cases) reported that their child had been hospitalized in the last six months.

Table 4. Health Utilization Rates Among Study Sample Children with and without Behavioral and/or Developmental Disorders, Cape Town, South Africa, 2009

<table>
<thead>
<tr>
<th></th>
<th>Number of Visits to a Clinic in the Last 6 Months</th>
<th>Number of Hospitalizations in the Last 6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td></td>
<td>Difference* (p)</td>
<td>Difference* (p)</td>
</tr>
<tr>
<td>Total Population</td>
<td>3 (2-6)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Cases</td>
<td>6 (3-9)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Controls</td>
<td>2 (1-4)</td>
<td>0 (0-0)</td>
</tr>
</tbody>
</table>

IQR=interquartile range
*Wilcoxon rank-sum test of equality of medians
DISCUSSION
Our findings suggest that current maternal alcohol consumption, binge drinking in the past six months, and alcohol use six months before pregnancy are significantly associated with childhood BDD within a study population in Cape Town, South Africa. The significant association between current drinking habits and outcome status has important implications for what is thought of as the impact of maternal alcohol consumption on BDD in children. Children with BDD were three times more likely to have mothers who currently drink and over 4.5 times more likely to have mothers who have binged in the past six months compared to control children (both associations were adjusted). There are two possible reasons for why current drinking status is associated with outcome status. First, mothers could drink alcohol as a coping mechanism for the stresses of taking care of a child with developmental or behavioral issues. More likely though, drinking status, especially binge drinking, can be considered a proxy for an unstable home environment and other social factors that could lead to, or exacerbate, behavioral issues in the children.

In light of the non-significant association between outcome status and gestational alcohol use, several points must be made. While previous research has found that South African women more readily admit to drinking alcohol than women in First-World settings,1 this study differs from that one in that it was conducted over ten years later among mothers and/or proxy respondents, instead of pregnant women attending antenatal clinics. Our study participants are likely more knowledgeable about the effects of drinking alcohol during pregnancy, making them more similar to women in First-World settings who tend to underreport gestational drinking due to embarrassment and stigmatization.2 Two patterns in the data support this conjecture: the difference between admission of drinking six months before pregnancy versus during pregnancy and the effect of using proxy respondents.

Proxy respondents were more likely than the biological mothers themselves to report maternal gestational period drinking. Approximately 40% of all case respondents admitted to consuming alcohol six months before the index pregnancy and approximately 20% admitted to alcohol use during the pregnancy. Among biological mother respondents for cases, rates for alcohol use six months before pregnancy and during pregnancy were 38% and 15% respectively; among proxy respondents for cases these rates were 47% and 33% respectively. The crude associations between gestational period drinking variables and outcome status may thus have been biased away from the null before controlling for use of a proxy respondent (Table 3). This supports the notion that the biological mothers interviewed for this study may have underreported their true alcohol consumption patterns.

We inquired about alcohol consumption six months before pregnancy under the presumption that women would more honestly report their pre-pregnancy drinking habits. These reports may be more indicative of drinking patterns during early stages of pregnancy, when much of the damage to the infant occurs,9 especially since some women are unaware that they are pregnant until a few weeks into the first trimester. In addition, we attempted to elicit accurate responses about gestational alcohol use through a backward timeline strategy used elsewhere.19,20 This study found a stronger association between children with BDD and drinking before pregnancy than with drinking during pregnancy, meaning that either the biological mothers truly cut back on alcohol use while pregnant, or, more likely, that they underreported their gestational drinking habits.

One factor that affected study results is the study setting. Cases and controls were very similar since both groups access clinics through RCH, a public tertiary level
facility. The screening questions we asked about the behaviors and social skills of the children may not have effectively excluded control children who could have undiagnosed disorders as a consequence of their complex health histories. Further, the biological mother or proxy respondent who answered the screening questions for controls may have underreported the existence of behavioral and social problems among their children.

In addition, RCH is heavily accessed by practicing Muslims, who, mostly, abstain from drinking alcohol for cultural reasons, thus the rates of alcohol consumption are lower than in other studies among South African women.1,17 We attempted to retrospectively ascertain the percentage of Muslim participants among cases and controls, but were not successful in finding a consistent method that would provide an accurate count, leaving this factor an unmeasured potential confounder.

Similar to use of a proxy respondent, we adjusted for age of the child due to its possible effects on the accuracy of respondents’ answers. Age of the child was considered on the basis that respondents would have a better memory of the biological mother’s gestational drinking habits for a four year old, the lower age limit for the study, than for a twelve year old child, the upper age limit for the study. We also investigated the impact of gender on the associations between outcome status and maternal alcohol use since there were more males than females included in our total study population and especially among the sample of behavioral disordered children (60.0% and 74.5% respectively). When controlling for gender, in addition to use of a proxy respondent and age of the child, the explored associations between maternal alcohol use and BDD, especially the odds of drinking six months before pregnancy, increased.

The difference between gender distributions among the cases and controls speaks to differential rates of behavioral disorders in males and females. Male children tend to be diagnosed with ADHD more frequently than female children.7 The role of gender in the associations between maternal alcohol consumption and gender is less clear. Current maternal alcohol habits could be related to gender in that the sex of a child could influence whether or not the mother drinks alcohol via differential attitudes toward parenting styles for boys and girls. This relates to the impact of social environment on behaviors and development of children.

It has been shown that adverse events in the gestational period, such as low birth weight, are associated with differential outcomes of behavioral disorders between males and females.27 This means that there could be a biological relationship between maternal gestational alcohol use and gender in that a fetus could be differentially susceptible to the effects of prenatal alcohol exposure depending on whether it is male or female. While our study sample supports this conjecture, this proposed association requires further research.

Health utilization
Data on health utilization in South Africa is limited and while it was not the main focus of this study, the findings suggest two important inferences. First, the median number of visits to an outpatient clinic in the last six months is significantly higher for children with BDD than without (6 and 2 respectively; p<0.001). Secondly, as our estimates are six-month rates, the average annual rates for planned clinic visits among cases and controls could be as high as 12 and 4 respectively, which are well above the national averages for PHC utilization in children five years and older (2.6),23 which has important implications for an increased burden on health services.
Our rates for clinic visits are likely exaggerated due to opportunistic sampling. While this method reduced the burden on participants of making a special trip to the clinic, it biased the study in that the participants are all children who reliably access health services, thus inflating the health utilization rates. Further, the specialized clinics accessed by cases require their patients to be reliably contactable so they may differ from the general population of the Western Cape, reducing the generalizability of this study’s results regarding health utilization.

Conversely, the fact that all of the study participants were recruited in health care facilities spoke to the validity of their responses regarding utilization. Many respondents used their appointment cards to recall their utilization over the last six months or easily recounted their six-month access rates because they bring their children for appointments on a regular schedule. In addition, most case and control children had not been hospitalized in the last six months, possibly due to the result that both groups regularly access health facilities and thus are less likely to be hospitalized.

The fact that both case and control children are regular users of the health system may have served to bias the results of this study towards the null regarding associations with prenatal alcohol exposure. The ages of the children included in this study ranged from 4 to 12 years, a decision made to better exclude confirmed cases of FASD, which is most accurately diagnosed between ages 3 and 10.\(^1\) This means that since children in our study regularly access health services, their FASD diagnosis should theoretically not have been missed. The key to further exploring an association between BDD and prenatal alcohol exposure is to access children who do not regularly utilize health services or who are outside of the health system entirely.

**Limitations**
Several limitations of this study are due to limits of our questionnaire. Background information on the mothers, including cultural background, education level, and employment status, should be collected. Data on cultural backgrounds, including religion and reasons for abstaining from alcohol, would help to better explain lowered drinking rates. This may also help to provide further insight into the strong association we observed between current maternal alcohol use and BDD in children, and whether it is a good marker of the impact of an unstable home environments on childhood BDD. A cohort study where the prenatal alcohol consumption status of mothers has been confirmed would help to investigate temporal issues surrounding the competing impact of current and gestational alcohol use on BDD in their children.

Future research on this topic would also benefit from open-ended questions specifically regarding alcohol consumption. While honesty of response cannot be controlled, open-ended questions regarding alcohol use would be conducive to eliciting more insightful and accurate reports. Many of the women offered reasons for not drinking or provided further insight into their drinking habits, but this was not quantifiable for the analysis. Providing a checklist or an open-ended question to capture this or other alcohol-related quantitative data would be a helpful improvement.

**CONCLUSIONS**
This study found clear evidence that current maternal alcohol consumption, especially binge drinking, is associated with childhood BDD. Similarly, BDD were associated with maternal alcohol use six months before pregnancy, but not during pregnancy, although this latter finding may have been due to under-reporting. While
this did not support our conjecture that mild BDD in children in the Western Cape could be undiagnosed alcohol-attributed disorders, it helped to shed light on some the important impact of current maternal alcohol use, as a possibly proxy for unstable home environments, on behavior and development of children. Future research on the impact of maternal alcohol use on childhood development should include such environmental factors.

While our health utilizations rates may be of limited generalizability to the general Western Cape population, what is important is the increased number of visits to a clinic by children with behavioral or developmental disorders. The additional burden on the health care system by children with these types of disorders warrants further research.

REFERENCES


APPENDIX A: Acknowledgements

I am extremely grateful to Leslie London for providing guidance and feedback during all stages of the research, especially for his advice in planning the study, data analysis, and writing. I am equally grateful to Colleen Adnams for her enthusiastic support and initiating contact with the various research sites.

This work could not have been completed without the cooperation and involvement of Dr. Rod Anderson, Dr. Nick Shortall, Sister Lesley Hoogervorst and all of the staff members of the Child and Family Unit and the Outpatient Department of Red Cross Children’s Hospital. Further, data collection would not have been possible without the language skills, sensitivity, and competence of Tracy, Shaheema, and Lungi.

This work was funded by a generous grant from the National Research Foundation (Grant 443296).
CONSENT FORM

Hello, my name is _______________________________ and I am from the University of Cape Town. I will be reading you a form that explains the purpose, risks, and benefits of participating in our research study to see if you are willing to participate.

Purpose of Research: This study is being done to see if drinking alcohol during pregnancy affects the behaviours and abilities of children. If you choose to participate, I will need to look through the medical records of the child with you today and to ask you some questions. Some of these questions will tell us if you are able to participate in the study or not. We hope the study findings will help us to learn more about drinking alcohol in pregnancy and also what to do about it.

Confidentiality: If you take part, none of your personal information will be written on the questionnaire, only a unique number will be written in the space provided. Your name and contact information will be written on a separate document that links you to your questionnaire. Only the researchers will have access to this data and it will be stored in a secure place where only the researchers will have access to the file.

Voluntary Participation: Participation in this study is your choice. Should you feel uncomfortable at any point, you are free to withdraw from the interview or refuse to answer a question. We understand it’s your choice and no one in the facility will treat you or you child differently if you decide you do not want to be part of the study.

Risks and Discomfort: You will not be at risk for any physical harm by completing this questionnaire. If you find any questions too sensitive to answer, you may choose to skip them or to withdraw from the interview.

Cost or Compensation: There will be no cost to participate, and if you are eligible to complete the questionnaire, you will be given a voucher to a supermarket when the interview is complete.

If you have any questions about the study or the questionnaire, you may ask the researchers present during the research. This study has been reviewed and approved by the University of Cape Town ethics committee. Further questions regarding the ethical standards of this research project may be directed to Dr. Mark Blockman, Head of the UCT Ethics Committee, at 021.406.6942.

This agreement states that you have received a copy of this informed consent. Your signature below shows that you agree to participate in this study.

_______________________       ______________________       _____________
Signature of Participant                        Subject name (print)                 Date

______________________           _______________________     _____________
Signature of Researcher                     Researcher name (print)                  Date
Participant Code: ____________

Interview facility: ________________________

Interviewer: ________________________

Date of interview: ________________________

---

QUESTIONNAIRE

Please mark or fill in the answers appropriately.

---

INFORMATION REGARDING THE CHILD:

QUESTIONS A-C SHOULD BE ADDRESSED TO PARENTS/CARETAKERS OF POTENTIAL CONTROLS ONLY.

First I would like to ask you some questions about this child to see if you are able to participate in our study.

A. In your opinion, does this child have trouble paying attention?
   
   [☐] Yes
   [☐] No

B. In your opinion, does this child have a hard time fitting into new social situations?
   
   [☐] Yes
   [☐] No

C. In your opinion, does this child behave at a level notably younger than his/her age?
   
   [☐] Yes
   [☐] No

1. Current age of child  

2. Gender of child

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
</tr>
</tbody>
</table>

3. What is your relationship to this child?

<table>
<thead>
<tr>
<th>Relationship</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological mother</td>
<td></td>
</tr>
<tr>
<td>Biological father</td>
<td></td>
</tr>
<tr>
<td>Adoptive parent</td>
<td></td>
</tr>
<tr>
<td>Foster parent</td>
<td></td>
</tr>
<tr>
<td>Caregiver</td>
<td></td>
</tr>
<tr>
<td>Relative</td>
<td></td>
</tr>
<tr>
<td>Friend</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

Please phrase the remaining questions according to the answer given for Number 3.

4a. During the last 6 months, has your/this child visited this or any other clinic or community health centre?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

4b. How many times has your/this child visited this or any other clinic or community health centre in the last 6 months including today?

5a. During the last 6 months, has your/this child visited a hospital?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

5b. How many times has your/this child visited a hospital in the last 6 months?

If yes to 5a, please continue with 5b and 5c. If not, proceed to the next section.
5c. Did any of these visits require your/this child to stay in the hospital overnight?

Yes
No

INFORMATION REGARDING BIOLOGICAL MOTHER OF THE CHILD:

I am now going to ask you questions about the biological mother of this child. If you are not the biological mother, please answer to the best of your ability.

NB: If the biological mother is NOT answering the questions, please phrase them accordingly.

1. Current age (of biological mother) __________

Now I'm going to ask you some questions about drinking alcohol:

2. Some people drink alcohol. Have you ever had a drink containing alcohol? / Has the biological mother ever had a drink containing alcohol?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Do not know</td>
<td></td>
</tr>
</tbody>
</table>

IF NO TO 2, END INTERVIEW HERE.

3. Do you drink alcohol now? / Does the biological mother drink alcohol now?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Do not know</td>
<td></td>
</tr>
</tbody>
</table>

IF NO TO 3, SKIP TO 6.

4. How much alcohol do you / does the biological mother drink on average during the weekdays?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No drinking during weekdays</td>
<td></td>
</tr>
<tr>
<td>Occasional weekday drinking, less than once every week</td>
<td></td>
</tr>
<tr>
<td>1-2 drinks per week every week</td>
<td></td>
</tr>
<tr>
<td>3-5 drinks per week every week</td>
<td></td>
</tr>
<tr>
<td>6-7 drinks per week every week</td>
<td></td>
</tr>
<tr>
<td>8 or more drinks per week every week</td>
<td></td>
</tr>
<tr>
<td>Do not know</td>
<td></td>
</tr>
</tbody>
</table>
5. How much alcohol do you / does the biological mother drink on average on weekends?

<table>
<thead>
<tr>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>No drinking during the weekend</td>
</tr>
<tr>
<td>Occasional weekend drinking, less than once every weekend</td>
</tr>
<tr>
<td>1-2 drinks per weekend every weekend</td>
</tr>
<tr>
<td>3-5 drinks per weekend every weekend</td>
</tr>
<tr>
<td>6-7 drinks per weekend every weekend</td>
</tr>
<tr>
<td>8 or more drinks per weekend</td>
</tr>
<tr>
<td>Do not know</td>
</tr>
</tbody>
</table>

6. In the last six months, did you/ she ever drink 5 drinks or more on one occasion?

<table>
<thead>
<tr>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Do not know</td>
</tr>
</tbody>
</table>

NB: FOR QUESTIONS 7-10: If the respondent currently drinks, use the first option. If the respondent is a past drinker, use the section option.

7. Have you/has she ever felt that you/ she should cut down on your/her drinking? OR

When you/she did drink alcohol, did you/she ever feel that you/she should cut down on your/her drinking?

<table>
<thead>
<tr>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Do not know</td>
</tr>
</tbody>
</table>

8. Have people annoyed you/ her by criticizing your/her drinking? OR

When you/she did drink alcohol, did people annoy you/her by criticizing your/her drinking?

<table>
<thead>
<tr>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Do not know</td>
</tr>
</tbody>
</table>


9. **Have you/ has she** ever felt bad or guilty about **your/her** drinking?  
   **OR**  
   When **you/she** did drink alcohol, did **you/she** ever feel bad or guilty about **your/her** drinking?  
   
<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Do not know</th>
</tr>
</thead>
</table>

10. **Have you/ has she** ever had a drink first thing in the morning to steady **your/her** nerves or get rid of a hangover?  
   **OR**  
   When **you/she** did drink alcohol, did **you/she** ever have a drink first thing in the morning to steady **your/her** nerves or get rid of a hangover?  
   
<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Do not know</th>
</tr>
</thead>
</table>

11a. In the 6 months before becoming pregnant with this child, did **you/ the biological mother** ever drink alcohol?  
   
<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Do not remember</th>
<th>Do not know</th>
</tr>
</thead>
</table>

   **IF YES TO 11a:**  

11b. How much did **you/she** drink on average during the 6 months before becoming pregnant with this child?  
   **IF SHE DRINKS NOW:**  
   
<table>
<thead>
<tr>
<th>Drank about the same as now</th>
<th>Drank less than now</th>
<th>Drank more than now</th>
<th>Do not remember</th>
<th>Do not know</th>
</tr>
</thead>
</table>

   **IF NOT A CURRENT DRinker:**  
   
   Occasional drinking, less than once every week  
   1-2 drinks per week every week  
   3-5 drinks per week every week  
   6-7 drinks per week every week  
   8 or more drinks per week every week  
   Do not remember  
   Do not know
12a. Did you/ the biological mother drink alcohol while pregnant with this child?

<table>
<thead>
<tr>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Do not remember</td>
</tr>
<tr>
<td>Do not know</td>
</tr>
</tbody>
</table>

**IF YES TO 12a:**

12b. If you/she drank alcohol while pregnant with this child, how much did you/she drink on average during the first trimester?

**IF SHE DRINKS NOW:**

<table>
<thead>
<tr>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drank about the same as now</td>
</tr>
<tr>
<td>Drank less than now</td>
</tr>
<tr>
<td>Drank more than now</td>
</tr>
<tr>
<td>Do not remember</td>
</tr>
<tr>
<td>Do not know</td>
</tr>
</tbody>
</table>

**IF NOT A CURRENT DRINKER:**

<table>
<thead>
<tr>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occasional drinking, less than once every week</td>
</tr>
<tr>
<td>1-2 drinks per week every week</td>
</tr>
<tr>
<td>3-5 drinks per week every week</td>
</tr>
<tr>
<td>6-7 drinks per week every week</td>
</tr>
<tr>
<td>8 or more drinks per week every week</td>
</tr>
<tr>
<td>Do not remember</td>
</tr>
<tr>
<td>Do not know</td>
</tr>
</tbody>
</table>
Ms. E. Katwan
UCT
elizabeth.katwan@gmail.com

Dear Ms. Katwan

**Project: Case-Control study of the association of use of health services by children with neurobehavioural disorders with prenatal alcohol exposure**

Thank you for your application to conduct research dated 24 March 2009.

Approval is granted to conduct the above-mentioned research at Red Cross War Memorial Children’s Hospital.

Yours faithfully,

Dr. T. Blake
Senior Medical Superintendent
09 February 2009

REC REF: 013/2009

Ms E Katwan
Public Health & Family Medicine

Dear Ms Katwan

PROJECT TITLE: CASE-CONTROL STUDY OF THE ASSOCIATION OF USE OF HEALTH SERVICES BY CHILDREN WITH NEUROBEHAVIOURAL DISORDERS WITH PRENATAL ALCOHOL EXPOSURE.

Thank you for submitting your study to the Research Ethics Committee for review.

The study is approved for one year until the 11th February 2010.

Several methodological and ethical concerns were identified but the reviewer does not feel that the study needs to be resubmitted to the Research Ethics Committee and has recommended that any changes be discussed with and approved by the supervisors.

Methodological comments:
It would be useful if the specific aim was more clearly stated earlier than page 6 of the proposal. It may be assumed that the title of the study indicates the aim but the title is also not clear. While there are clearly good estimates of alcohol use in pregnancy in the Western Cape, if one is trying to find the association of health service use with prenatal alcohol exposure, is it not necessary to be able to trace prenatal alcohol exposure as well as alcohol use in a particular setting, population or sample? This would include children who with prenatal alcohol exposure but who do not utilise services. It seems that the study question really is: Do children with FASD require and utilise health services more than children who do not have FASD but have developmental delay? [The latter is assumed as the control group is chosen from children seen at the Child Health Unit, but this may be an erroneous assumption] There are some additional queries that require clarification in the text, please refer to the notes in the submitted proposal. These are all issues of clarity rather than substantive.

In the interview schedule we suggest that you re-look at whether questions 3-4 are needed. They are an abrupt entry and may be answered negatively in initial defence, thus closing down any further options for the respondent to answer specifics. It seems that there are sufficient opportunities in the rest of the questions to get the answers to these.
Ethical comments:
The referral mentioned in 'D. Beneficence' needs to be more definitive. This is a particularly vulnerable population group and one can assume that mothers or caregivers need support. Please establish particular access to support. 'Local mental health services' are notoriously over-burdened and waiting lists are long. This is not adequate after eliciting information which could directly trigger the need for professional or social support.

Please make sure that the informed consent forms are also available in Afrikaans and Xhosa (if relevant); and please can you make them more user-friendly to maximise the possibility of informed consent. Please see suggestions on the attached consent form.

Please submit an annual progress report if the research continues beyond the expiry date or let us have a brief summary of your findings if the research is completed within the approval period.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

[Signature]

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulations Part 50, 56 and 312.
American Journal of Public Health (AJPH) Instructions for Authors

“What AJPH Authors Should Know”

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Editorial Board Chair: Hector Balcazar, PhD
Images of Health

*Images of Health* aims to train the eye as well as the mind. We hope that the provocative pictures, posters, and graphics displayed here will inspire readers to ask, What makes an image effective? What images might enhance current or future public health initiatives or materials? How might the power of pictures be harnessed to improve the public’s health? Department Editors Theodore Brown ([theodore_brown@urmc.rochester.edu](mailto:theodore_brown@urmc.rochester.edu)) and Elizabeth Fee ([elizabeth_fee@nlm.nih.gov](mailto:elizabeth_fee@nlm.nih.gov)) edit historical *Images of Health* columns, and Image Editor Aleisha Kropf ([slappyalk@gmail.com](mailto:slappyalk@gmail.com)) edits contemporary *Images of Health* columns.

*Example of an historical Images of Health Column:*


*Example of a contemporary Images of Health Column:*


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*Example of brief:*


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**Example of research and practice article:**


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The title page should include the title of the manuscript only. Authors names should be deleted to ensure double blinding of the paper during the peer review process.

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Structured abstracts are required for research and practice articles and should not exceed 180 words (headings not included). Structured abstracts employ 4 headings: Objectives, Methods, Results, and Conclusions. Please see the AMA Manual of Style, 10th Edition for further guidance on structured abstracts.

Headings

Heads should conform to a consistent pattern, using no more than 3 outline levels, and should be kept brief. Avoid acronyms, sentences, and question marks. Research and practice articles and briefs must use the following level-1 section heads: Methods, Results, and Discussion.

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Each table and figure should be self-contained. The title should be fully comprehensible without reference to the main text, as should any terminology or variable within the main body or footnote of the table or figure. New references cited within a table or figure should be numbered as though they fall at the first callout, i.e., mention, of that table or figure in the main text of the paper. For example, if Table 1 is called out just after reference 64, the references in Table 1 will start at 65.

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Further, be careful to describe relative risks accurately, because common errors can confuse the reader. For example, an odds ratio of 4.79 indicates that the outcome in question is almost 5 times as likely to occur, compared with the reference condition, and indicates a nearly 4-fold increase in risk, not a nearly 5-fold increase in risk.

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Source:


Date of Revision: July 7, 2009