JECH Online First, published on October 19, 2009 as 10.1136/jech.2009.091785

Title Page: A new method of prenatal alcohol classification accounting for dose, pattern, and timing of exposure: Improving our ability to examine fetal effects from low to moderate alcohol.

Authors: Colleen M O'Leary, Carol Bower, Steve R Zubrick, Elizabeth Geelhoed, Jennifer J Kurinczuk, Natasha Nassar

Type of manuscript: Original Article

Authors' names and affiliations:
Ms. Colleen M **O'Leary** BSc, MPH
Division of Population Sciences, Telethon Institute for Child Health Research
Centre for Child Health Research, University of Western Australia, Perth, WA, Australia
colleeno@ichr.uwa.edu.au

Professor Carol **Bower** MBBS, PhD
Division of Population Sciences, Telethon Institute for Child Health Research
Centre for Child Health Research, University of Western Australia, Perth, WA, Australia
carolb@ichr.uwa.edu.au

Professor Stephen R **Zubrick** MSc, PhD
Curtin University of Technology
Centre for Developmental Health
Perth, WA, Australia
steve@ichr.uwa.edu.au

Professor Elizabeth **Geelhoed** PhD MPH BEc
School of Population Health
University of Western Australia
Perth, WA 6009, Australia
Elizabeth.Geelhoed@uwa.edu.au

Dr. Jennifer J **Kurinczuk** MSc(Epid), MD
National Perinatal Epidemiology Unit
University of Oxford, Old Road Campus
Headington, Oxford, OX3 7LF, UK
jenny.kurinczuk@npeu.ox.ac.uk

Dr. Natasha **Nassar** BEc, MPH, PhD
Division of Population Sciences, Telethon Institute for Child Health Research
Centre for Child Health Research, University of Western Australia, Perth, WA, Australia
natashan@ichr.uwa.edu.au

Corresponding Author
Ms. Colleen O'Leary

Telethon Institute for Child Health Research
PO Box 855, West Perth WA 6872, Australia
Phone: +61 (08) 9489-7941, Fax: +61 (08) 9489-7700
colleeno@ichr.uwa.edu.au

Keywords
Ethanol D02.033.375; Pregnancy G08.686.785.760.769; Methods [E05.581]; Maternal Behavior [F01.829.263.370.215]; Child Development [F01.525.200]

Abstract

Background: When examining the association between prenatal alcohol exposure and fetal effects, epidemiological studies have ignored the timing and intensity of the exposure. This study investigates the effect of using *dose, pattern and timing* of consumption ('composite' method) for examining the association between prenatal alcohol exposure and fetal effects.

Methods: The 'composite' method resulted in six categories of exposure (abstinent, low, moderate, binge <weekly, binge 1-2x/week and heavy). The odds of language delay and child behaviour problems were calculated for the 'composite' method and then compared with an analysis using averaged estimates of <1 and 1+ drinks per day and with stratification by quantity ignoring dose per occasion. Data used for the analyses are from a 10% random sample of non-Indigenous women delivering a live infant in Western Australia (1995-1996) who were invited to participate in an 8-year longitudinal survey (78% response rate n=2,224; 85% were followed-up at two-years, 73% (five-years), 61% (eight-years)).

Results: The effect of moderate and binge levels of exposure was only evident with the 'composite' method; anxious/depressed problems following first trimester moderate exposure OR 2.24. (95% CI 1.16;4.34) and following late pregnancy moderate (aggressive behaviour OR 1.93 (0.91-4.09)) and binge (language delay OR 3.00 (0.90;9.93)) exposures. Results for heavy levels of exposure were similar with each method. The estimates for late pregnancy were imprecise due to small numbers.

Conclusion
The 'composite' method of classification more closely reflects real life drinking patterns and better discriminates maternal drinking than the other methods, particularly low, moderate and binge levels.

Introduction

Despite almost four decades of research, the nature of the dose-response relationship between prenatal alcohol exposure (PAE) and fetal effects remains unclear. Importantly, we have yet to determine if there is a level of alcohol which is not harmful to the developing fetus.[1] Over two decades ago dose and timing of PAE were highlighted as important research questions[2] and since then, animal studies have identified that the impact on the fetus from PAE is subject to the timing and intensity of the exposure.[3, 4] Yet these factors have been overlooked in alcohol and human pregnancy research.

One important issue is that the methods used to quantify PAE have not reflected real life maternal drinking patterns and prevent a clear examination of the dose-response relationship between PAE and fetal effects. Many epidemiological studies have used an averaged daily estimate of alcohol consumed during pregnancy,[5-7] in some cases averaged across pregnancy,[6] while other studies have stratified by the number of alcoholic drinks per week, described either as standard drinks[8-10] or grams of alcohol.[11] These methods are insensitive to the dose of alcohol consumed per occasion and the frequency of consumption which affect the intensity of fetal exposure. While adverse effects have been demonstrated at doses of alcohol as low as an average of 0.5 ounces (oz) of absolute alcohol (AA) (one standard drink) per day [12, 13] and <0.3 ounces AA/day averaged across pregnancy,[6] it is recognized that few women drink more than 4 days per week during pregnancy indicating that the dose of alcohol on drinking days may be considerably higher than an average estimate indicates.[13]

This paper presents a method of quantifying PAE which takes into account the *dose, pattern and timing* of maternal alcohol consumption, which we have called the 'composite' method. The estimates of PAE obtained with the 'composite' estimate are then compared, using population-based data, with estimates of PAE reported in the literature, an averaged daily quantity and a measure stratifying by grams per week. The effectiveness of the three methods for detecting an association between PAE and fetal effects are then compared. We have used the results of studies investigating the association between PAE, using the 'composite method' and each of language delay[14] and child behaviour problems,[15] and then re-analysed the data using an averaged estimate of PAE and stratification by grams per week.

Methods

Study population

In Western Australia (WA) between 1995-1997 a 10% random sample of all women delivering a live infant were invited by letter at 12 weeks postpartum to participate in a postal survey designed to investigate health-related behaviours and events before and during pregnancy and in early infancy (Figure 1).[16-18] Mothers whose infants were given up for adoption (n=5) were excluded. Aboriginal mothers were being recruited into a more culturally appropriate study being run concurrently and were not invited to participate.

Figure 1: Flow diagram of RASCALS longitudinal study selection criteria for the Language Delay and CBCL analyses

Respondents were representative of mothers of all singleton live births in WA with the exception of a slight under-representation of mothers with low birth weight babies (5.3% overall versus 4.7% respondents) and mothers aged less than 20 years (6.0% overall versus 3.6% respondents).[17,[19]]

From the 1995 and 1996 cohorts (n=4007), a 70% random sample of mothers of singletons (n = 2,837) was invited to participate in a longitudinal postal follow-up known as the RASCALS (Randomly Ascertained Sample of Children born In Australia's Largest State) study (Figure 1). Participants in the longitudinal study had a slightly higher income, were more likely to be married and had higher levels of maternal education compared with non-participants.[18, 20, 21] There was no marked differential loss to follow-up across alcohol exposure groups (unpublished data). None of the children in the cohort had received a diagnosis of Fetal Alcohol Syndrome at any point from birth to 8 years of age.

Ethics approval for the conduct of this study was granted by the Princess Margaret Hospital Research Ethics Committee and the WA Confidentiality of Health Information Committee.

Table 1: Coding of Alcohol Measures for Each Type of Beverage

	Grams of Alcohol*			
Measure	**Beer****	**Wine**	**Spirits**	**Fortified Wine**
Glass	7	15	20	9
Middy§	10	-	-	-
Can	15	-	15†	-
Stubby§	15	-	-	-
Pint	10	-	-	-
Bottle	30	70	250	112.5
1/2 Bottle	15	35	125	-
Carafe	-	50	-	-
Wine Cask/Box	-	360	-	-
Wine Cooler	-	10	-	-
Nip	-	-	10	9

* Australian Standard Drink = 10 grams of Alcohol
**Full Strength Beer; † Pre-mixed spirits drinks; § Australian measures

Maternal Alcohol Consumption

The questions about maternal alcohol consumption were asked 3-months post-partum and data were collected for each trimester separately. Women were asked to indicate how often they drank alcohol (5 or more, 3-4 or 1-2 days per week; 1-2 days per month; less than once per month; or never), and the quantity consumed (e.g., number of cans, glasses, bottles) on a typical occasion for each of the four types of alcoholic beverages (beer, wine/champagne, spirits/liqueurs and fortified wines) for each trimester.[17] Standard drink calculations were derived during the data analysis stage, according to the quantities specified in Table 1.[22]

'Composite' Method of Classifying Prenatal Alcohol Exposure

To examine the effect of the *dose, pattern, and timing* of PAE on fetal and child outcomes, maternal alcohol consumption was categorised by combining the total quantity, dose per occasion, and frequency, which we have called the 'composite' method. The 'composite' method was classified into five mutually exclusive groups for each trimester of pregnancy: 'low', 'moderate', 'binge less frequently than weekly (binge is classified as the consumption of 50+ grams of alcohol per occasion)'; 'binge 1-2 times per week (referred to as weekly)'; and 'heavy' (Table 2). The maximum alcohol intake in each respective period was used to assign the level of drinking. Where alcohol consumption was missing for the third trimester (n=27), the second trimester alcohol consumption information was assigned. The referent group comprised women who reported abstaining throughout pregnancy.

The 'low' category was defined in line with the 2001 Australian National Health and Medical Research Council Alcohol Guideline No. 11 for women who are pregnant or might soon become pregnant, which states that *"If women choose to drink, over a week, should have less than 7 standard drinks, AND, on any one day, no more than 1-2 standard drinks (10-20 grams per occasion)"*.[22] One standard drink in Australia is equal to 10 grams of alcohol. The 'moderate' group included women drinking <=70 grams of alcohol per week with the majority consuming between 21 to 49 grams per occasion (Table 2). Theoretically, if a woman had consumed only one standard drink each day (70 grams/week) she was included in the moderate group but in fact all these women were drinking more than one drink per occasion. The difference between the quantity of alcohol consumed by women classified in the low and moderate categories

Table 2: Alcohol Consumption during Pregnancy for Measures of Alcohol using Total Dose, Dose per Occasion, and Frequency, for Women Who Consumed Alcohol During Pregnancy

		'Composite' Alcohol Groups				
		Low	Moderate‡	Binge <Weekly	Binge 1-2x/Week	Heavy
Grams* per Week				**Grams/week**		
Trimester 1	**Mean**	6.2	16.6	16.8	97.3	192.5
	Median	2.5	8.0	15.0	82.0	150.0
	Minimum	0.5	2.1	5.0	50.0	71.0
	Maximum	60.0	67.5	61.0	270.0	1453.0
Trimester 2	**Mean**	6.0	14.6	14.7	92.5	161.1
	Median	2.5	7.5	10.6	68.5	120.0
	Minimum	0.5	2.1	5.0	50.0	75.0
	Maximum	60.0	66.0	43.3	265.0	540.0
Trimester 3	**Mean**	6.0	15.2	15.4	95.5	143.2
	Median	2.5	7.6	13.6	90.0	105.0
	Minimum	0.5	3.0	5.0	50.0	74.0
	Maximum	60.0	70.0	37.5	265.0	540.0
Grams* per Occasion		**(%)**	**(%)**	**(%)**	**(%)**	**(%)**
Trimester 1	**<=10**	21.2	N/A	N/A	N/A	N/A
	11 to 20	78.8	1.6	N/A	N/A	17.6
	21 to 49	N/A	98.4	N/A	N/A	53.7
	50+	N/A	N/A	100.0	100.0	28.7
Trimester 2	**<=10**	18.7	N/A	N/A	N/A	N/A
	11 to 20	81.3	1.1	N/A	N/A	18.2
	21 to 49	N/A	98.9	N/A	N/A	59.1
	50+	N/A	N/A	100.0	100.0	22.7
Trimester 3	**<=10**	18.4	N/A	N/A	N/A	N/A
	11 to 20	81.6	1.5	N/A	N/A	24.6
	21 to 49	N/A	98.5	N/A	N/A	60.9
	50+	N/A	N/A	100.0	100.0	14.5
Frequency per Week		**(%)**	**(%)**	**(%)**	**(%)**	**(%)**
Trimester 1	**<Weekly†**	78.6	68.6	100.0	N/A	N/A
	1-2x/Week	18.7	28.9	N/A	100.0	6.5
	>2x/Week	2.7	2.5	N/A	N/A	93.5
Trimester 2	**<Weekly†**	79.8	73.3	100.0	N/A	N/A
	1-2x/Week	17.6	25.1	N/A	100.0	N/A
	>2x/Week	2.5	1.6	N/A	N/A	100.0
Trimester 3	**<Weekly†**	79.9	70.4	100.0	N/A	N/A
	1-2x/Week	17.3	27.6	N/A	100.0	1.4
	>2x/Week	2.8	2.0	N/A	N/A	98.6

*10 grams= 1 Standard drink in Australia and 50 grams/occasion = binge drinking; † <Weekly = once

every 8-10 weeks up to 1-2 times per month; ‡ Moderate group contains women consuming 10 grams of alcohol per occasion daily.

related only to the number of standard drinks consumed per occasion; 1-2 and 3-4 per occasion respectively. Binge drinking (50 grams or more per occasion) was divided into <weekly and 1-2x/week. The 'heavy' group included women drinking >70 grams with a frequency of at least weekly or more often, with the majority of women consuming more than 20 grams of alcohol per occasion. Women binge drinking more than twice/week were included in this group. A small number of women (n=7 in first trimester and n=1 in third trimester) reported drinking 1-2 times per week and reported consuming two or more types of beverages, each at less than 50 grams/occasion but with a total weekly consumption of 70 grams or higher. As we could not be confident that the women had consumed only once per week, and therefore at binge levels, we coded them as heavy drinkers.

The 'composite' method of quantifying maternal alcohol consumption was compared with three published methods of calculating PAE including, (1) an average daily quantity of alcohol exposure averaged per trimester; (2) average daily alcohol exposure averaged over the whole pregnancy (the weekly quantity of alcohol reported by each woman for each trimester of pregnancy combined and then divided by 3); and (3) average weekly amount (grams) of alcohol consumed categorised into 4 categories: 0.1-12.0, 12.1-24.0, 24.1-48.0, >48.0 grams per week.[10] The average daily quantity of maternal alcohol consumption calculated for Methods 1 and 2 was then dichotomized for each trimester. A weekly quantity of less than 70 grams of alcohol consumed was classified as <1 standard drink per day; and 70 grams of alcohol or more consumed per week classed as 1 or more standard drinks per day.

Analyses Comparing the 'Composite' Method with Traditional Methods of Classifying Prenatal Alcohol Exposure

Descriptive data for prenatal alcohol consumption in each trimester were calculated. Comparisons between methods of quantifying maternal alcohol consumption were made using contingency table analysis. Data analyses were conducted using SPSS version 15.0.

We examined the effect of PAE, defined using the 'composite' method of quantification and the three methods described above, on: (1) language delay in two-year old children[14] and (2) child behaviour problems (somatic complaints, anxiety/depression and aggressive behaviour.[15] Due to sample size limitations we were not able to examine each of the six alcohol categories for both of these studies. In particular, for the study on child behaviour problems binge drinking occurring 1-2 times per week or less frequently could not be analysed separately due to small numbers. The descriptions of combined groupings are given below.

The association between prenatal alcohol exposure and odds of language delay was estimated using a multiple imputation procedure using SAS PROC MI (SAS Institute Inc., 2004) and logistic regression using SAS 9.1 (PROC LOGISTIC and PROC

MIANALYZE)[23] to generate odds ratios and 95% confidence intervals. Just over three-quarters (76.5%) of the covariates had <=2% missing data and 23.5% had between 2.1% to <4% missing data. Four alcohol categories in the 'composite' method were examined: abstinent, low, moderate-heavy and binge <weekly to 1-2x/week for each trimester separately. Covariates included in the model were: maternal factors (maternal age, parity, education, marital status, smoking, illicit drug use and depression, anxiety and stress as measured by the Depression Anxiety Stress Scale[24, 25]) and family factors (income, presence of partner in household, parenting ability[26] and family functioning[27]).

To investigate the association between prenatal alcohol and clinically significant child behaviour problems, longitudinal analysis of children followed-up at 2, 5, and 8-years of age was undertaken using generalized estimating equation (GEE) analysis using dichotomised T-scores obtained from the Child Behaviour Checklist.[28] GEE takes into account the longitudinal design of the study with the analysis of repeated measurements on a given individual and allows examination of the effects of time, the differences between groups, and the difference between groups over time.[29]

Four categories in the 'composite' method were examined: abstinent, low, moderate (including women 'binge drinking less frequently than weekly) and heavy (including women who were binge drinking 1-2x/week or more often). Analyses for moderate drinkers were repeated following exclusion of <weeky binge drinkers. The outcomes were examined for first trimester exposure and for late pregnancy, defined as the maximum alcohol intake occurring in either second and/or third trimester. The analyses were adjusted for antenatal covariates (maternal age, marital status, parity, ethnicity, income, maternal smoking and use of illicit drugs, tranquilizers, and sleeping tablets during pregnancy) and postnatal covariates collected at each follow-up (marital status, income, treatment for postnatal depression, maternal depression (Beck Depression Inventory),[30] family functioning (McMaster Family Assessment Device),[27] parenting style (Parenting Scale),[26] tension in the family due to alcohol and maternal depression, anxiety and stress collected at the year 2 survey (Depression Anxiety and Stress Scale (DASS)).[25]

Self-reported income was available for 83% of the original cohort in the antenatal period and 96% to 98% of the cohort at each follow-up. Where income was missing in the antenatal period (17% of subjects), a socio-economic indicator based on area of residence was applied as a proxy measure.[31]

Results

Over one-third (36.1%) of women abstained from alcohol throughout pregnancy; 17% did not drink in first trimester but drank in either the second and/or third trimesters, and 8% of women consumed alcohol in first trimester but abstained in late pregnancy.

Maternal alcohol consumption for each of the five categories, as defined by the 'composite' method, is described in Table 2. The quantity of alcohol consumed by women classified as low, moderate or less than weekly binge drinkers varied little

across pregnancy. On the other hand, the quantity of alcohol consumed by women drinking at binge levels once to twice per week decreased from the first to second trimester (median 82 grams to 68.5 grams) increasing to 90 grams in trimester 3. For women drinking at heavy levels the quantity decreased across pregnancy (median 150 grams in the first trimester to 105 grams in the third trimester) and there was a marked decrease in the percentage of women consuming 5+ drinks per occasion (28.7% in first trimester to 14.5% in third trimester). The frequency of drinking remained relatively constant across pregnancy for each of the alcohol consumption groups.

Table 3: Comparison of daily alcohol consumption for each trimester of pregnancy (Method 1) and the 'composite' measure of maternal alcohol consumption.

Daily Consumption Averaged within Trimesters	Percentage of women in each averaged alcohol group (%)				
	Low	Moderate	Binge <Weekly	Binge 1-2x/Week	Heavy
			Trimester 1		
<1 std drink/day	71.4	24.0	3.4	1.2	0.0
1 or more std drinks/day	0.0	0.0	0.0	29.4	70.6
			Trimester 2		
<1 std drink/day	79.0	18.8	1.6	0.6	0.0
1 or more std drinks/day	0.0	0.0	0.0	15.4	84.6
			Trimester 3		
<1 std drink/day	79.4	19.1	1.2	0.3	0.0
1 or more std drinks/day	0.0	0.0	0.0	13.8	86.3

Daily Consumption Averaged within Trimesters	Percentage of women in each 'composite'* alcohol group (%)				
	Low	Moderate	Binge <Weekly	Binge 1-2x/Week	Heavy
			Trimester 1		
<1 std drink/day	100.0	100.0	100.0	32.8	0.0
1 or more std drinks/day	0.0	0.0	0.0	67.2	100.0
			Trimester 2		
<1 std drink/day	100.0	100.0	100.0	50.0	0.0
1 or more std drinks/day	0.0	0.0	0.0	50.0	100.0
			Trimester 3		
<1 std drink/day	100.0	100.0	100.0	35.3	0.0
1 or more std drinks/day	0.0	0.0	0.0	64.7	100.0

*'Composite' method using quantity, frequency, and dose of alcohol per occasion.

When maternal alcohol consumption was averaged for each trimester (Method 1) and dichotomized into <1 and 1+ standard drink per day, all women classified as drinking at low, moderate, and binge drinking <weekly by the 'composite' method were included in the <1 standard drink per day category (Table 3). Women classified as heavy drinkers were included in the higher category of 1+ standard drinks per day. However, it is notable that for women who binged at least weekly or more often (less than 1% of all women drinking in pregnancy), almost a third (32.8%) of women in first trimester (50.0% and 35.3% in second and third trimesters, respectively) were classified as consuming <1 standard drink per day.

Table 4: Comparison of daily alcohol consumption averaged across pregnancy (Method 2) and the 'composite' measure of maternal alcohol consumption.

Daily Consumption of Alcohol	Percentage of women in each averaged alcohol group (%)				
Averaged across Pregnancy**	**Low**	**Moderate**	**Binge <Weekly**	**Binge 1-2x/Week**	**Heavy**
			Trimester 1		
<1 std drink/day	68.9	22.8	3.2	2.8	2.2
1 or more std drinks/day	3.4	7.9	1.1	14.6	73.0
			Trimester 2		
<1 std drink/day	79.0	18.5	1.5	0.6	0.5
1 or more std drinks/day	3.7	8.5	3.7	15.9	68.3
			Trimester 3		
<1 std drink/day	79.2	18.6	1.1	0.4	0.7
1 or more std drinks/day	7.2	14.5	2.4	10.8	65.1
Daily Consumption of Alcohol	**Percentage of women in each 'composite'* alcohol group (%)**				
Averaged across Pregnancy**	**Low**	**Moderate**	**Binge <Weekly**	**Binge 1-2x/Week**	**Heavy**
			Trimester 1		
<1 std drink/day	99.8	98.4	98.4	80.6	39.8
1 or more std drinks/day	0.2	1.6	1.6	19.4	60.2
			Trimester 2		
<1 std drink/day	99.8	98.1	90.6	45.8	15.2
1 or more std drinks/day	0.2	1.9	9.4	54.2	84.8
			Trimester 3		
<1 std drink/day	99.6	97.0	92.3	47.1	21.7
1 or more std drinks/day	0.4	3.0	7.7	52.9	78.3

*'Composite' method using quantity, frequency, and dose of alcohol per occasion.

**The daily consumption when averaged across pregnancy gives one value representing the average quantity of alcohol consumed per day for each woman during her pregnancy.

Averaging maternal alcohol consumption across pregnancy (Method 2), showed little discrimination between drinking patterns with the category of <1 standard drink per day containing women drinking at each of the five 'composite' categories (Table 4). Notably, 5.0% of women in this group were drinking at either binge weekly or heavy levels, as defined by the 'composite' method, in first trimester. In third trimester, 24.1% of women classified as drinking 1+ standard drink per day were drinking at low, moderate, or binge <weekly levels as defined by the 'composite' method. This misclassification resulted in 80.6% of women who were binge drinking 1-2x/week and 39.8% of heavy drinkers in first trimester defined as drinking <1 standard drink per day. However, these percentages decreased to about 46%-47% for binge drinking 1-2x/week in second and third trimesters and to 15.2% and 21.7% for heavy drinkers in second and third trimesters respectively.

Comparison of the method of stratifying alcohol intake into four categories by grams/week (Method 3) with the 'composite' method of classifying maternal alcohol consumption showed a lack of discrimination between low, moderate, and binge less than weekly levels of consumption (Table 5). Although the majority (around 83%) of women drinking at low levels were classified in the 0.1-12 gram category, a large percentage of women drinking at moderate (64-70%) and binge <weekly (33-50%) were also classified into this group. The next two groups, 12.1-24 and 24.1-48 grams, also contained a mixture of women classified as drinking at low, moderate, and binge less than weekly by the 'composite' method. Women binge drinking 1-2x/week and heavy drinking were all classed into the 48+grams category.

Table 5: Comparison of alcohol consumption grams per week (Method 3) and the 'composite' measure of maternal alcohol consumption.

Grams Alcohol per Week	The Percentage of women within alcohol consumption grams/week				
	Low	Moderate	Binge <Weekly	Binge 1-2x/Week	Heavy
			Trimester 1		
0.1 – 12 grams	78.6	20.0	1.4	0.0	0.0
12.1 – 24 grams	79.4	9.3	11.3	0.0	0.0
24.1 – 48 grams	26.6	70.3	3.1	0.0	0.0
48.1+ grams	6.0	13.4	0.0	31.3	49.3
			Trimester 2		
0.1 – 12 grams	83.3	15.8	0.8	0.0	0.0
12.1 – 24 grams	89.4	7.1	3.5	0.0	0.0
24.1 – 48 grams	43.1	53.4	3.4	0.0	0.0
48.1+ grams	8.1	16.2	0.0	16.2	59.5
			Trimester 3		
0.1 – 12 grams	83.4	16.3	0.3	0.0	0.0
12.1 – 24 grams	85.6	11.3	3.1	0.0	0.0
24.1 – 48 grams	42.9	55.4	1.8	0.0	0.0
48.1+ grams	5.4	13.5	0.0	13.5	67.6
Grams Alcohol per Week	**Percentage of women in each 'composite'* alcohol group (%)**				
	Low	**Moderate**	**Binge <Weekly**	**Binge 1-2x/Week**	**Heavy**
			Trimester 1		
0.1 – 12 grams	82.0	64.4	38.1	0.0	0.0
12.1 – 24 grams	14.2	5.1	52.4	0.0	0.0
24.1 – 48 grams	3.1	25.4	9.5	0.0	0.0
48.1+ grams	0.7	5.1	0.0	100.0	100.0
			Trimester 2		
0.1 – 12 grams	82.9	69.1	50.0	0.0	0.0
12.1 – 24 grams	12.5	4.3	30.0	0.0	0.0
24.1 – 48 grams	4.1	22.3	20.0	0.0	0.0
48.1+ grams	0.5	4.3	0.0	100.0	100.0
			Trimester 3		
0.1 – 12 grams	83.6	69.9	33.3	0.0	0.0
12.1 – 24 grams	12.5	7.1	50.0	0.0	0.0
24.1 – 48 grams	3.6	19.9	16.7	0.0	0.0
48.1+ grams	0.3	3.2	0.0	100.0	100.0

*'Composite' method using quantity, frequency, and dose of alcohol per occasion.

The comparison of the various methods of classification in the analysis of language delay among 2-year old children is presented in Table 6. Using the 'composite' method a 3-fold non-significant increase in language delay was observed in association with binge drinking <weekly up to 1-2x/week following alcohol exposure in either second ((adjusted) aOR 3.00 (95% CI 0.90;9.93)) or third trimester (aOR 3.02 (95% CI 0.75;12.20)).[14] No association was seen with PAE averaged within trimesters (Method 1) or while averaging PAE across pregnancy (Method 2). The classification of PAE by grams/week (Method 3) produced inconsistent results. The odds of language delay increased with PAE between 12.1-24.0 grams in each trimester by 61% to 85% (aOR 1.85; 95% CI 1.03;3.34 for third trimester exposure). However, there was no dose-response relationship. The adjusted odds in the lower and higher alcohol exposure categories were close to unity, ranging from 0.55-1.45.

The results of GEE analyses of the relationship between PAE and child behaviour problems (anxious/depressed, somatic, and aggressive problems) are shown in Table 7. Analyses using the 'composite' method, showed heavy levels of PAE in first trimester increased the odds of anxious/depressed problem behaviours (aOR 2.82; 95%CI 1.07, 7.43) and somatic complaints (aOR 2.74 (95% CI 1.47;5.12)). Similar results for anxious/depressed problems were also seen following moderate PAE (aOR 2.24 (95% CI 1.16;4.34)) and remained similar when <weekly binge drinking was excluded (aOR 2.49 (95% CI 1.26;4.93). The increased odds of aggressive behaviour following heavy exposure (aOR 1.92 (0.74-5.01)) were not observed when the analysis was restricted to women drinking only in first trimester (results not shown).[15] Each of the methods averaging PAE showed similar increased odds of behaviour problems following exposure to 1+ standard drinks or exposure to 48.1+ grams/week and increased odds of somatic complaints were evident following exposure to 24.1-48 grams of alcohol/week in method 3 (Table 7). Late pregnancy heavy PAE increased the odds of aggressive behaviour(s) (aOR 2.92 (95% CI 0.85;10.09)), as did moderate levels of exposure (aOR 1.93 (95% CI 0.91-4.09)). The results for moderate exposure were similar following exclusion of <weekly binge drinking (aOR 2.05 (95% CI 0.96;4.37).[15] Each of the methods averaging PAE showed similar increased odds of aggressive behaviour(s) following exposure to 1+ standard drinks or exposure to 48.1+ grams/week (Table 7).

Table 6: Odds of Language Delay in 2-year-old children following Prenatal Alcohol Exposure: Comparison of the various methods of classifying maternal alcohol consumption

	Adjusted‡ Odds Ratio (95% CI)		
Prenatal Alcohol	**Trimester 1**	**Trimester 2**	**Trimester 3**
Abstinent throughout pregnancy*	1.00	1.00	1.00
'Composite' Method			
Low	0.97 (0.65;1.43)	0.87 (0.59;1.28)	0.84 (0.57;1.23)
Mod-Heavy	0.71 (0.40;1.27)	1. 26 (0.63;1.74)	1.50 (0.90;2.49)
Binge**	1.49 (0.60;3.73)	3.00 (0.90;9.93)	3.02 (0.75;12.20)
Method 1: Averaged Within Trimesters			
<1 standard drink/day†	0.89 (0.64;1.23)	0.92 (0.67;1.27)	0.92 (0.67;1.27)
1+ standard drink/day†	1.38 (0.56;3.41)	0.65 (0.14;2.95)	0.52 (0.12;2.33)
Method 2: Averaged Across Pregnancy	**(Trimesters do not apply)**		
<1 standard drink/day†		0.92 (0.67;1.28)	
1+ standard drink/day†		1.19 (0.39;3.63)	
Method 3: Grams per Week	**Trimester 1**	**Trimester 2**	**Trimester 3**
0.1 – 12 grams	0.76 (0.54;1.09)	0.77 (0.54;1.09)	0.86 (0.61;1.21)
12.1 – 24 grams	1.61 (0.88;2.95)	1.85 (0.99;3.45)	1.85 (1.03;3.34)
24.1 – 48 grams	0.55 (0.19;1.56)	1.41 (0.65;3.02)	0.78 (0.30;2.05)
48.1+ grams	1.45 (0.68;3.09)	0.91 (0.30;2.76)	1.41 (0.54;3.65)

*Referent group for each analysis; **Binge = 5+ per occasion **<**Weekly to 1-2 days/week; †Standard drink =10 grams alcohol. ‡Adjusted for maternal factors (maternal age, parity, education, marital status, smoking, illicit drug use and depression, anxiety and stress (DASS)) and family factors (income, presence of partner in household, parenting ability and family functioning).

Table 7: Odds of Child Behaviour Problems in 2, 5, and 8-year-old children following prenatal alcohol exposure: Comparison of estimates of maternal alcohol consumption

	Adjusted Odds Ratio (95% CI)					
	1st Trimester			Late Pregnancy		
Prenatal Alcohol	**Anxious/Depressed**	**Somatic**	**Aggressive**	**Anxious/Depressed**	**Somatic**	**Aggressive**
Abstinent throughout pregnancy*	1.00	1.00	1.00	1.00	1.00	1.00
'Composite' Method						
Low	1.06 (0.59-1.88)	0.82 (0.55-1.22)	0.98 (0.52-1.82)	1.21 (0.72-2.02)	0.82 (0.56-1.19)	1.06 (0.59-1.92)
Moderate	2.24 (1.16-4.34)	1.07 (0.61-1.88)	1.06 (0.49-2.28)	1.52 (0.72-3.19)	1.08 (0.63-1.86)	1.93 (0.91-4.09)
Heavy	2.82 (1.07-7.43)	2.74 (1.47-5.12)	1.92 (0.74-5.01)	0.43 (0.06-3.28)	1.82 (0.79-4.17)	2.92 (0.85-10.09)
Method 1: Averaged Within Trimesters						
<1 standard drink/day†	1.35 (0.82-2.23)	0.87 (0.60-1.27)	0.99 (0.56-1.76)	1.29 (0.80-2.08)	0.87 (0.61-1.24)	1.27 (0.73-2.20)
1+ standard drink/day†	2.87 (0.98-8.35)	3.36 (1.80-6.26)	2.27 (0.84-6.17)	-	2.15 (0.96-4.80)	2.29 (0.56-9.37)
Method 2: Averaged Across Pregnancy	**(Trimesters do not apply)**			**(Trimesters do not apply)**		
<1 standard drink/day†	1.20 (0.76-1.90)	0.86 (0.61-1.21)	1.15 (0.69-1.93)	-	-	-
1+ standard drink/day†	1.74 (0.45-6.73)	3.60 (1.81-7.17)	2.69 (0.79-9.21)	-	-	-
Method 3: Grams per/Week	1st Trimester			Late Pregnancy		
0.1 – 12 grams	1.32 (0.78-2.26)	0.79 (0.53-1.19)	1.04 (0.57-1.89)	1.27 (0.77-2.10)	0.90 (0.63-1.30)	1.36 (0.78-2.39)
12.1 – 24 grams	1.52 (0.60-3.86)	0.91 (0.45-1.86)	0.83 (0.26-2.67)	1.16 (0.42-3.22)	0.42 (0.18-1.01)	0.79 (0.24-2.62)
24.1 – 48 grams	1.29 (0.37-4.53)	2.10 (1.04-4.25)	0.90 (0.20-4.11)	1.37 (0.49-3.78)	1.22 (0.61-2.45)	0.62 (0.12-3.30)
48.1+ grams	2.36 (0.99-5.61)	2.15 (1.16-4.00)	1.67 (0.67-4.17)	0.67 (0.17-2.72)	1.80 (0.83-3.92)	2.37 (0.79-7.09)

*Referent group for each analysis; †Standard drink = 10 grams alcohol. ‡Adjusted for antenatal covariates (maternal age, marital status, parity, ethnicity, income, maternal smoking and use of illicit drugs, tranquilizers, and sleeping tablets during pregnancy) and postnatal covariates collected at each follow-up (marital status, income, treatment for postnatal depression, postnatal depression (Beck Depression Inventory), family functioning (McMaster Family Assessment Device), parenting style (Parenting Scale), tension in the family due to alcohol and maternal depression, anxiety and stress collected at the year 2 survey (DASS)).

Discussion

The 'composite' method of classifying maternal alcohol consumption provides a detailed classification of PAE that reflects both maternal drinking patterns and the dose of alcohol to which the fetus is exposed. Importantly accounting for dose and pattern, in the classification of PAE using the 'composite' method, permits differentiation between low, moderate and binge patterns of drinking. Many previously published methods of classifying PAE have not accounted for these two factors[5-10] and few have accounted for timing of exposure.[14, 32, 33] These are important distinctions since the evidence indicates that different patterns of drinking will result in a very different blood alcohol content[34] and that it is the peak blood alcohol concentration, which governs the risk to the fetus.[3, 12, 35]

Compared with the 'composite' method, classifying maternal alcohol consumption by averaging PAE over trimester (Method 1) or over pregnancy (Method 2) to a daily intake, or categorising consumption by quantity alone (Method 3) obscured the real pattern of drinking. The lack of discrimination led to some women who were actually drinking at heavy levels being classified in the lower dose category and vice versa. This limits our ability to estimate the level of risk particularly from exposure to low, moderate, or binge drinking <weekly which were generally grouped together.

Ignoring the dose, pattern, and timing of PAE may in some circumstances, such as language delay, completely mask the association that was observed using the 'composite' method. In investigations of child behaviour problems each method demonstrated the association at the highest category but only the 'composite' method allowed for a detailed examination of the dose response.

All studies that collect self-reported data on maternal alcohol consumption during pregnancy are subject to the risk of reporting bias. It is well recognised that reporting of prenatal alcohol consumption is influenced by the method and the timing of the questions.[13, 36] Although the 'composite' method was based on data collected retrospectively and will not fully overcome these limitations, we believe the use of the 'composite' method of classifying PAE minimises the risk of misclassification of exposure.

Many studies will have collected detailed information on maternal alcohol consumption in order to calculate the averaged estimates of PAE. A useful step would be to reanalyse data using a 'composite' method to classify PAE in order to determine the effect of dose, pattern, and timing of exposure on infant and child outcomes.

A limitation of the 'composite' method is that as only a small percentage of women drink in late pregnancy, particularly at binge and heavy levels, large numbers of women will be required to provide sufficient power to adequately determine the relationship between higher levels of alcohol exposure and fetal effects. Where there is sufficient similarity in methods used to collect information

on maternal drinking during pregnancy, collaboration between researchers and the pooling of data may overcome sample size limitations.

Conclusion

Our findings demonstrate that averaging maternal alcohol consumption or stratifying exposure without accounting for dose, pattern, and timing of consumption prevents investigation of dose and response. In particular, it masks the assessment of the effect of low, moderate, and binge drinking on infant and child outcomes. The adoption of a 'composite' method that more closely reflects real life drinking patterns and that allows for capture of aspects of dose, pattern, and timing of alcohol consumption, may avoid obscuring important relationships and reduce the likelihood of either over-stating or under-stating aspects of risk to the developing fetus.

Figure 1: Flow diagram of RASCALS longitudinal study selection criteria for the Language Delay and CBCL analyses

Conflict of Interest

The authors declare that they have no conflict of interest in relation to this paper.

Funding

The Western Australian survey of health related behaviours and events during pregnancy and early infancy was funded by grants from Healthway (the Western Australian Health Promotion Foundation (#94/2705, #96/49078, #98/8016)) to whom we are most grateful.

This study was supported by the Australian National Health and Medical Research Council (NHMRC) program grant number 353514 (2005-09), NHMRC Research Fellowship (353628) (Dr Bower) and NHMRC Public Health (Australia) Fellowship (404118) (Dr Nassar). Dr Kurinczuk was partially funded by a National Public Health Career Scientist award from the Department of Health and National Health Services Research and Development (NCC RCD) (PHCS022) when this analysis was conducted.

Acknowledgements

The authors declare that there is no conflict of interest in relation to this article. The authors thank Margaret Wood and Peter Cosgrove for maintenance of the databases and Peter Jacoby for statistical advice in generalized estimating equations. The authors thank the staff of the WA Data Linkage Unit for access to the WA Data Linkage System and for their assistance in obtaining the data, and the WA Health Data Custodians for access to the core health datasets. We are very grateful to the parents who have participated in the RASCALS study and for the support of the Telethon Institute for Child Health Research; in particular the RASCALS study team.

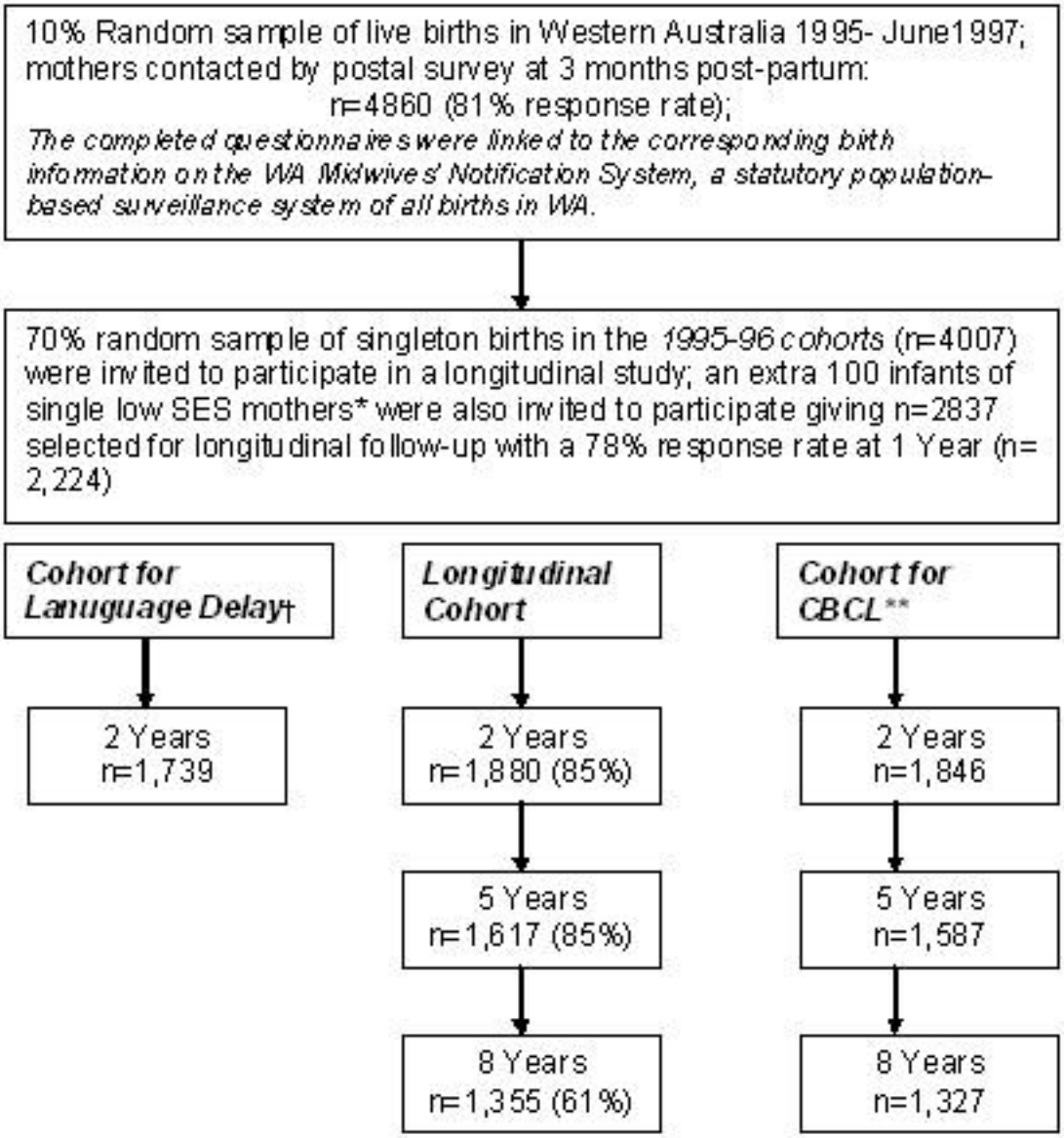
References:

1. Henderson J, Gray R, Brocklehurst P. Systematic review of effects of low-moderate prenatal alcohol exposure on pregnancy outcome. *BJOG* 2007; **114**(3):243-252.
2. Rosett H, Weiner L. Prevention of fetal alcohol effects. *Pediatrics* 1982; **69**(6):813-6.
3. Matthews SG. Early programming of the hypothalamo-pituitary-adrenal axis. *Trends Endocrinol Metab* 2002; **13**(9):373-80.
4. Clarren SK, Astley SJ, Gunderson VM, Spellman D. Cognitive and behavioral deficits in nonhuman primates associated with very early embryonic binge exposures to ethanol. *J Pediatr* 1992; **121**(5):789-796.
5. Ernhart CB, Sokol RJ, Ager JW, Morrow-Tlucak M, Martier S. Alcohol-related birth defects: assessing the risk. *Ann N Y Acad Sci* 1989; **562**:159-72.
6. Sood B, Delaney-Black V, Covington C, Nordstrom-Klee B, Ager J, Templin T, et al. Prenatal alcohol exposure and childhood behavior at age 6 to 7 years: I. dose-response effect. *Pediatrics* 2001; **108**(2):E34.
7. Little RE, Weinberg CR. Risk factors for antepartum and intrapartum stillbirth. *Am J Epidemiol* 1993; **137**(11):1177-89.
8. Marbury M, Linn S, Monson R, Schoenbaum S, Stubblefield P, Ryan K. The association of alcohol consumption with outcome of pregnancy. *Am J Public Health* 1983; **73**(10):1165-8.
9. Olsen J, Rachootin P, Schiodt AV. Alcohol use, conception time, and birth weight. *J Epidemiol Community Health* 1983; **37**(1):63-5.
10. Kesmodel U, Wisborg K, Olsen S, Henriksen T, Secher N. Moderate alcohol intake during pregnancy and the risk of stillbirth and death in the first year of life. *Am J Epidemiol* 2002; **155**(4):305-12.
11. Olsen J, da Costa Pereira A, Olsen SF. Does Maternal Tobacco Smoking Modify the Effect of Alcohol on Fetal Growth? *Am J Public Health* 1991; **81**(1):69.
12. Jacobson JL, Jacobson SW. Prenatal alcohol exposure and neurobehavioural development: where is the threshold? *Alcohol Health Res World* 1994; **18**(1):30-37.
13. Jacobson SW, Chiodo LM, Sokol RJ, Jacobson JL. Validity of maternal report of prenatal alcohol, cocaine, and smoking in relation to neurobehavioral outcome.[see comment]. *Pediatrics* 2002; **109**(5):815-25.
14. O'Leary C, Zubrick SR, Taylor CL, Dixon G, Bower C. Prenatal Alcohol Exposure and Language Delay in Two-Year Old Children: The importance of dose and timing on risk. *Pedatrics* 2009; **123**(2):547-554.
15. O'Leary CM, Nassar N, Kurinczuk JJ, Bower C. Evidence of a complex association between dose, pattern, and timing of prenatal alcohol exposure and child behavior problems *Addiction* Accepted for publication 2009, *in press*.
16. Kurinczuk JJ, Parsons DE, Dawes V, Burton PR. The relationship between asthma and smoking during pregnancy. *Women & Health* 1999; **29**(3):31-47.

17. Colvin L, Payne J, Parsons DE, Kurinczuk JJ, Bower C. Alcohol consumption during pregnancy in non-Indigenous west Australian women. *Alcohol Clin Exp Res* 2007; **31**(2):276-84.
18. Straker LM, Pollock CM, Zubrick SR, Kurinczuk JJ. The association between information and communication technology exposure and physical activity, musculoskeletal and visual symptoms and socio-economic status in 5-year-olds. *Child: Care, Health & Development* 2006; **32**(3):343-351.
19. Stanley FJ, Read AW, Kurinczuk JJ, Croft ML, Bower C. A population maternal and child health research database for research and policy evaluation in Western Australia. *Semin Neonatol* 1997; **2**:195-201.
20. Hall WA, Zubrick SR, Silburn SR, Parsons DE, Kurinczuk JJ. A model for predicting behavioural sleep problems in a random sample of Australian pre-schoolers. *Infant Child Dev* 2007; **16**(5):509-523.
21. Zubrick SR, Taylor CL, Rice ML, Slegers DW. Late language emergence at 24 months: An epidemiological study of prevalence, predictors, and covariates. *J Speech Lang Hear Res* 2007; **50**(December):1562-1592.
22. National Health and Medical Research Council. Australian Alcohol Guidelines: Health risks and Benefits. Canberra: NHMRC; 2001.
23. SAS Institute Inc. SAS/STAT 9.1 user's guide. Cary, NC: SAS Institute Inc; 2004.
24. Lovibond PF, Lovibond SH. The structuve of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behavior Research and Therapy.* 1995; **33**:335-343.
25. Lovibond SH, Lovibond PF. Manual for the Depression Anxiety Stress Scales (2nd ed.). Sydney, Australia: Psychology Foundation Monograph; 1995.
26. Arnold DS, O'Leary SG, Wolff LS, Archer MM. The Parenting Scale: A measure of dysfunctional parenting in discipline situations. *Psychol Assess* 1993; **5**(2):137-144.
27. Miller IW, Epstein NB, Bishop DS, Keitner GI. The McMaster family assessment device: reliability and validity. *J Marital Fam Ther* 1985; **11**(4):345-356.
28. Achenbach TM, Edelbrock C. Manual for the Child Behavior Checklist/2-3 and 1992 profile. Burlington, VT: University of Vermont; 1991.
29. Armitage P, Berry G, Matthews J. Statistical Methods in Medical Research. 4th ed: Blackwell Publishing; 2002.
30. Beck A, Steer R, Brown G. Manual for Beck Depression Inventory II (BDI-II). San Antonio, Texas: Psychology Corporation; 1996.
31. ABS. Socio-Economic Indexes for Areas. Canberra: Australian Bureau of Statistics; 2001 January 2004. Report No.: ABS Catalogue No. 2039.0.
32. O'Leary CM, Nassar N, Kurinczuk JJ, Bower C. The effect of maternal alcohol consumption on fetal growth and preterm birth. *BJOG* 2009; **116**(3):390-400.
33. Sayal K, Heron J, Golding J, Alati R, Davey Smith G, Gray R, et al. Binge pattern of alcohol consumption during pregnancy and childhood mental health

outcomes: Longitudinal populaiton-based study. *Pedatrics* 2009; **123**(2):e289-e296.
34. Fisher HR, Simpson RI, Kapur BM. Calculation of blood alcohol concentration (BAC) by sex, weight, number of drinks and time. *Can J Public Health* 1987; **78**(5):300-4.
35. Henderson J, Kesmodel U, Gray R. Systematic review of the fetal effects of prenatal binge-drinking. *J Epidemiol Community Health* 2007; **61**(12):1069-1073.
36. Alvik A. Consistency of reported alcohol use by pregnant women: Anonymous versus confidential questionnaires with item nonresponse differences. *Alcohol Clin Exp Res* 2005; **29**(8):1444-1449.

Figure 1: Flow diagram of RASCALS longitudinal study selection criteria for the Language Delay and CBCL analyses



*It was anticipated that the loss-to-follow-up of these women would be high and so extra numbers were included to increase the likelihood that reasonable numbers would continue in the study over time.

†Exclusions for Language Delay analysis: Children from non–English-speaking households, or households in which languages other than English were spoken (n =116), and children with severe disabilities and syndromal conditions known to be on the causal pathway of language delay or disorder (n = 25).** Exclusions for the study on child behaviour using the Child Behaviour Checklist (CBCL): Children with severe disability/syndromal conditions (2-years n=25 and at 5 and 8-years n=22), Children with an Aboriginal father (2-years n= 9, 5-years n= 8, and 8-years n= 6).