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

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ABSTRACT

Background When examining the association between prenatal alcohol exposure and fetal effects, the timing and intensity of exposure have been ignored in epidemiological studies. The effect of using dose, pattern and timing of consumption ("composite" method) was investigated in this study, to examine 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 1–2×/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 were from a 10% random sample of non-Indigenous women delivering a live infant in Western Australia (1995–1997). Participants from the 1995-1996 cohort were invited to participate in an 8-year longitudinal survey (78% response rate n=2224; 85% were followed-up at 2 years, 73% at 5 years and 61% at 8 years).

Results The effect of moderate and binge levels of exposure was only evident with the composite method; anxiety/depression following first-trimester moderate exposure (OR 2.24, 95% CI 1.16 to 4.34), and following late pregnancy moderate (aggressive behaviour OR 1.93, 95% CI 0.91 to 4.09) and binge (language delay OR 3.00, 95% CI 0.90 to 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.

Despite almost 4 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 that is not harmful to the developing fetus.[1] Over two decades ago, dose and timing of PAE were highlighted as important research questions[2]; since then, animal studies have identified that the impact of PAE on the fetus is subject to the timing and intensity of the exposure.[3 4] Yet, these factors have been overlooked in alcohol and human pregnancy research.

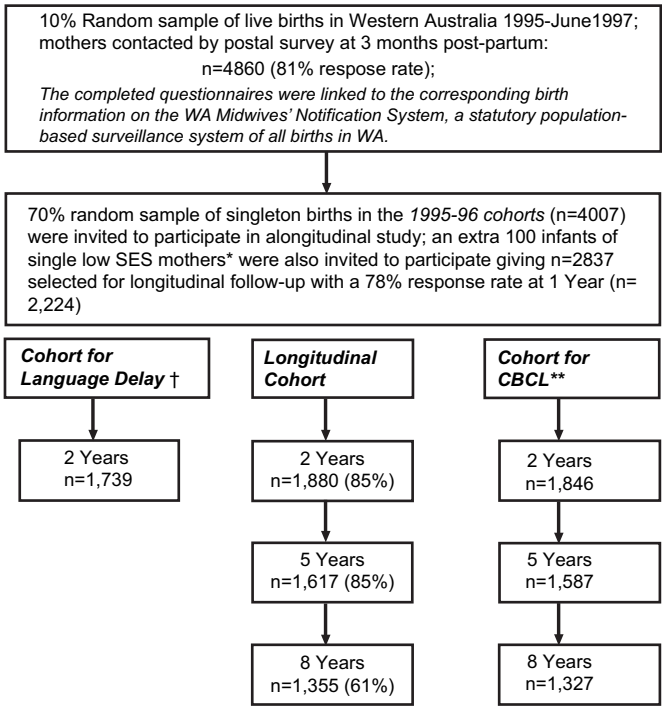
One important issue is that the methods used to quantify PAE have not reflected real-life maternal drinking patterns, which prevent a clear examination of the dose–response relationship between PAE and fetal effects. Many epidemiological studies have used an averaged daily estimate of alcohol consumed 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 that 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 of absolute alcohol (one standard drink) per day[12 13] and <0.3 ounces absolute alcohol per day averaged across pregnancy,[6] it is recognised 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 article presents a method of quantifying PAE that 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 reanalysed the data using an averaged estimate of PAE and stratification by grams per week.

METHODS

Study population

In Western Australia between 1995 and 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.



*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 casual 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).

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 Western Australia, with the exception of a slight under-representation of mothers with low birthweight babies (5.3% overall vs 4.7% respondents) and mothers aged <20 years (6.0% overall vs 3.6% respondents).[17 19]

From the 1995 and 1996 cohorts (n=4007), a 70% random sample of mothers of singletons (n=2837) 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.

Maternal alcohol consumption

The questions about maternal alcohol consumption were asked 3 months postpartum, 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 (eg, number of cans, glasses or 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]

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 g of alcohol.
†Full-strength beer.
‡Premixed spirit drinks.
§Australian measures.

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+ g 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 g per occasion)".[22] One standard drink in Australia is equal to 10 g of alcohol. The moderate group included women drinking ≤70 g of alcohol per week, with the majority consuming between 21 and 49 g per occasion (table 2). Theoretically, if a woman had consumed only one standard drink each day (70 g/week), she was included in the moderate group; however, 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 related only to the number of standard drinks consumed per occasion: 1–2 and 3–4 per occasion, respectively. Binge drinking (50 g or more per occasion) was divided into <weekly and 1–2×/week. The heavy group included women drinking >70 g per week, with a frequency of at least weekly or more often, with the majority of women consuming more than 20 g 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 g/occasion but with a total weekly consumption of 70 g 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.

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				
Grams* per week		Low	Moderate‡	Binge <weekly Grams/week	Binge 1–2×/ week	Heavy
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
	1–2×/Week	18.7	28.9	N/A	100.0	6.5
	>2×/Week	2.7	2.5	N/A	N/A	93.5
Trimester 2	<Weekly†	79.8	73.3	100.0	N/A	N/A
	1–2×/Week	17.6	25.1	N/A	100.0	N/A
	>2×/Week	2.5	1.6	N/A	N/A	100.0
Trimester 3	<Weekly†	79.9	70.4	100.0	N/A	N/A
	1–2×/Week	17.3	27.6	N/A	100.0	1.4
	>2×/Week	2.8	2.0	N/A	N/A	98.6

*10 g=1 standard drink in Australia and 50 g/occasion=binge drinking.
†<Weekly=once every 8–10 weeks up to 1–2 times per month.
‡Moderate group contains women consuming 10 g of alcohol per occasion daily.
§N/A, not applicable.

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) daily alcohol exposure averaged over the whole pregnancy (the weekly quantity of alcohol reported by each woman for each trimester of pregnancy combined, divided by 3, and then divided by 7); and (3) an average weekly amount (grams) of alcohol consumed categorised into four categories: 0.1–12.0, 12.1–24.0, 24.1–48.0 and >48.0 g per week.[10] The average daily quantity of maternal alcohol consumption calculated for methods 1 and 2 was then dichotomised for each trimester. A weekly quantity of less than 70 g of alcohol consumed was classified as <1 standard drink per day, and 70 g of alcohol or more consumed per week classed as one 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 2-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 ORs and 95% CIs. 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 1–2×/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 generalised estimating equation analysis using dichotomised t scores obtained from the Child Behaviour Checklist.[28] A generalised estimating equation 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 1–2×/week or more often). Analyses for moderate drinkers were repeated following exclusion of <weekly 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, tranquilisers 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)).[24 25]

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

RESULTS

More than 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 82–68.5 g), increasing to 90 g in the third trimester. For women drinking at heavy levels, the quantity decreased across pregnancy (median 150 g in the first trimester to 105 g in the third trimester), and there was a marked decrease in the percentage of women consuming 5+ drinks per occasion (28.7% in the first trimester to 14.5% in the third trimester). The frequency of drinking remained relatively constant across pregnancy for each of the alcohol consumption groups.

When maternal alcohol consumption was averaged for each trimester (method 1) and dichotomised into <1 and 1+ standard drink per day, all women classified as drinking at low, moderate and binge <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 one-third (32.8%) of women in the first trimester (50.0% and 35.3% in the second and third trimesters, respectively) were classified as consuming <1 standard drink per day.

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 1–2×/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 1–2×/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.

Averaging maternal alcohol consumption across pregnancy (method 2) showed little discrimination between drinking patterns with the category of <1 standard drink per day including women drinking at each of the five composite categories (table 4). Notably, 5% of women in this group were drinking at either binge weekly or heavy levels, as defined by the composite method, in the first trimester. In the 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 1–2×/week and 39.8% of heavy drinkers in the first trimester defined as drinking <1 standard drink per day. However, these percentages decreased to about 46–47% for binge drinking 1–2×/week in the second and third trimesters and to 15.2% and 21.7% for heavy drinkers in the 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 g 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 g, also contained a mixture of women classified as drinking at low, moderate, and binge less than weekly by the composite method. Women binge drinking 1–2×/week and heavy drinking were all classed into the 48+ g category.

The comparison of the various methods of classification in the analysis of language delay among 2-year-old children is

Table 4 Comparison of daily alcohol consumption averaged across pregnancy (method 2) and the composite measure of maternal alcohol consumption

Daily consumption of alcohol Averaged across pregnancy†	Percentage of women in each averaged alcohol group (%)				
	Low	Moderate	Binge <weekly	Binge 1–2×/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 Averaged across pregnancy†	**Percentage of women in each composite* alcohol group (%)**				
	Low	**Moderate**	**Binge <weekly**	**Binge 1–2×/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.

Table 5 Comparison of alcohol consumption grams per week (method 3) and the composite measure of maternal alcohol consumption

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

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

presented in table 6. Using the composite method, a threefold non-significant increase in language delay was observed in association with binge drinking <weekly up to 1−2×/week following alcohol exposure in either the second (adjusted OR (aOR) 3.00, 95% CI 0.90 to 9.93) or third trimester (aOR 3.02, 95% CI 0.75 to 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 and 24.0 g in each trimester by 61−85% (aOR 1.85, 95% CI 1.03 to 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 to 1.45.

The results of generalised estimating equation analyses of the relationship between PAE and child behaviour problems (anxiety/depression, somatic problems and aggressive behaviour) are shown in table 7. Analyses using the composite method showed heavy levels of PAE in the first trimester, increasing the odds of anxiety/depression (aOR 2.82, 95% CI 1.07 to 7.43) and somatic complaints (aOR 2.74, 95% CI 1.47 to 5.12). Similar results for anxiety/depression were also seen following moderate PAE (aOR 2.24, 95% CI 1.16 to 4.34) and remained similar when <weekly binge drinking was excluded (aOR 2.49, 95% CI 1.26 to 4.93). The increased odds of aggressive behaviour following heavy exposure (aOR 1.92, 95% CI 0.74 to 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+ g/week, and increased odds of somatic complaints were evident following exposure to 24.1−48 g 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 to 10.09), as did moderate levels of exposure (aOR 1.93, 95% CI 0.91 to 4.09). The results for moderate exposure were similar following exclusion of <weekly binge drinking (aOR 2.05, 95% CI 0.96 to 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+ g/week (table 7).

DISCUSSION

The composite method of classifying maternal alcohol consumption provides a detailed classification of PAE that reflects 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 that 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; however, 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 that 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 to calculate the averaged estimates of PAE. A useful step would be to reanalyse data using a composite method to classify PAE to determine the effect of dose, pattern and timing of exposure on infant and child outcomes.

Table 6 Odds of language delay in 2-year-old children following prenatal alcohol exposure: comparison of various methods of classifying maternal alcohol consumption

	Adjusted§ OR (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 to 1.43)	0.87 (0.59 to 1.28)	0.84 (0.57 to 1.23)
Moderate—heavy	0.71 (0.40 to 1.27)	1.26 (0.63 to 1.74)	1.50 (0.90 to 2.49)
Binge†	1.49 (0.60 to 3.73)	3.00 (0.90 to 9.93)	3.02 (0.75 to 12.20)
Method 1: averaged within trimesters			
<1 std drink/day‡	0.89 (0.64 to 1.23)	0.92 (0.67 to 1.27)	0.92 (0.67 to 1.27)
1+ std drink/day‡	1.38 (0.56 to 3.41)	0.65 (0.14 to 2.95)	0.52 (0.12 to 2.33)
Method 2: averaged across pregnancy	(Trimesters do not apply)		
<1 std drink/day‡	0.92 (0.67 to 1.28)		
1+ std drink/day‡	1.19 (0.39 to 3.63)		
Method 3: grams per week (g)	Trimester 1	Trimester 2	Trimester 3
0.1—12	0.76 (0.54 to 1.09)	0.77 (0.54 to 1.09)	0.86 (0.61 to 1.21)
12.1—24	1.61 (0.88 to 2.95)	1.85 (0.99 to 3.45)	1.85 (1.03 to 3.34)
24.1—48	0.55 (0.19 to 1.56)	1.41 (0.65 to 3.02)	0.78 (0.30 to 2.05)
48.1+	1.45 (0.68 to 3.09)	0.91 (0.30 to 2.76)	1.41 (0.54 to 3.65)

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

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

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

*Referent group for each analysis.
†Standard drink=10 g alcohol.
‡Adjusted for antenatal covariates (maternal age, marital status, parity, ethnicity, income, maternal smoking and use of illicit drugs, tranquilisers 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),[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)[24 25]).

What is already known on this subject

Heavy prenatal alcohol exposure is accepted as a risk factor for fetal development. However, we are less clear about the effects from low and moderate exposure and this uncertainty has allowed a range of interpretations to be drawn, polarising health professional and consumer opinions. Methodological issues have contributed to our limited understanding; in particular, there has been no standardised method for classifying prenatal alcohol exposure that simultaneously accounts for the dose, pattern and timing of exposure.

What this study adds

The composite method of classifying prenatal alcohol reflects realistic drinking patterns and separates low, moderate and binge levels of prenatal exposure. The estimates of effect demonstrated with the composite method at moderate and binge levels were not evident when the analyses were conducted using traditional methods of classification. Not accounting for dose, pattern and timing may explain some of the variation in research findings.

consumption may avoid obscuring important relationships and reduce the likelihood of either overstating or understating aspects of risk to the developing fetus.

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