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REVIEW

THE EFFECTS OF PRENATAL ALCOHOL EXPOSURE ON INFANT MENTAL DEVELOPMENT: A META-ANALYTICAL REVIEW

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Abstract — **Aims:** Although research on fetal alcohol exposure has had a significant effect on social norms and public policy, there has been little quantitative review of this literature. **Methods:** Meta-analysis was used to examine the effects of prenatal alcohol exposure on infant mental development, assessed using the Mental Development Index (MDI) from the Bayley Scales of Infant Development, a widely used, standardized measure. The current study examined the effects of three levels of average daily exposure during pregnancy: less than 1 drink per day, 1–1.99 drinks per day and 2 or more drinks per day. Analyses were conducted separately for effects derived from observations of 6–8-, 12–13- and 18–26-month-old children. **Results:** Fetal alcohol exposure at all three dosage levels was associated with significantly lower MDI scores among 12–13-month-olds. The effect was attenuated, but not eliminated, when effect sizes adjusted for relevant covariates were used. For younger and older children, the effect of fetal alcohol exposure did not attain statistical significance at any dosage level. **Conclusions:** This pattern of results may reflect differences in MDI item content at different ages and the differential sensitivity of these abilities to prenatal alcohol exposure. Because the body of relevant literature is neither large nor conclusive, and because of heterogeneity in measurement, analysis and samples, caution is urged in interpreting results. Future research would benefit from use of more specific measures of infant outcomes and consideration of the impact of relevant covariates, different dosage patterns and timing of drinking on infant mental development.

INTRODUCTION

In 1968, Lemoine, Harousseau, Borteyru and Menuet first described a pattern of anomalies occurring in the offspring of alcohol-abusing mothers (Lemoine *et al*., 1968). Later dubbed Fetal Alcohol Syndrome (FAS) by Jones and Smith (1973), the syndrome includes growth deficiency, facial anomalies and neurological abnormalities. Since that time, research has examined the effects of prenatal alcohol exposure on a range of outcomes, including miscarriage, birth weight, physical anomalies, cognition and behaviour. This research has had a major impact on public policy, particularly in the United States, which mandates warning labels on all alcoholic beverages and where pregnant women who drink alcohol have been prosecuted (Armstrong and Abel, 2000).

Although there have been numerous qualitative reviews of the literature on prenatal alcohol effects (e.g. Coles *et al*., 1987; Little and Wendt, 1991; Forrest *et al*., 1992; Coles, 1993; Larkby and Day, 1997), meta-analytical reviews have rarely been undertaken (for exceptions see Makarechian *et al*., 1998; Polygenis *et al*., 1998). Meta-analysis offers several advantages over traditional qualitative literature reviews in the precision, objectivity and replicability of the analysis (Mullen, 1989). For example, whereas qualitative reviews typically rely on the significance of findings of individual studies without considering the magnitude of the relationship between variables, meta-analysis permits the computation of effect size estimates across multiple studies and formal testing of hypothesized moderator variables (Rosenthal and DiMatteo, 2001). We believe that this type of evaluation can be helpful both in interpreting existing research findings and in guiding future research efforts and public policy. For example, meta-analytical reviews of the impact of prenatal cocaine exposure on physical and mental development have challenged commonly held beliefs that cocaine universally results in severely impaired 'crack babies' (Lutiger *et al*., 1991; Lester *et al*., 1998).

The current review examined evidence for an effect of fetal alcohol exposure on infant mental development, as assessed by the Mental Development Index (MDI) of the Bayley Scales of Infant Development (BSID; Bayley, 1969). This instrument was designed to measure the developmental status of children ranging in age from 2 to 30 months, and is the most widely used, standardized measure of general infant development available to date. Although the measure has since been revised (BSID-II; Bayley, 1993), all of the studies included in the current meta-analysis used the original BSID. The Mental Scale assesses various aspects of development, such as sensory discrimination, eye–hand coordination, object permanence, receptive and expressive language, and rudimentary problem-solving abilities, appropriate for the developmental age of the child. The scale content changes with increasing child age. Whereas scale content at 6 months consists of items measuring sensorimotor development, at 12 months the measure incorporates spatial relations, short-term memory, attention, rudimentary problem-solving and receptive language. At 18 and 24 months, the scale content changes to incorporate symbolic functioning and language development, both receptive and expressive. Thus, the scale administered to a 6-month-old is not the same scale administered to a 12- or 24-month-old. Because the scale is normed, the Mental Scale raw scores are converted to standard scores called the MDI, with a mean of 100 and an SD of 16.

We chose to focus our meta-analysis of prenatal alcohol exposure on studies using infant MDI scores for theoretical as well as practical reasons. Mental development outcomes are likely to be critical for long-term functioning, especially if scores are extreme or more than 1 SD above or below the

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mean (Coles, 1992; Connor and Streissguth, 1996). Practically speaking, there are several published studies examining the mental development of infants using the BSID, with fewer studies examining the outcomes of older children. Furthermore, studies of older children have used a wide range of measures of both IQ and other specific cognitive abilities (e.g. attention, language, school performance), making comparisons across studies difficult. In contrast, the majority of studies of infants have used the MDI, thereby facilitating comparison across studies.

The current meta-analysis was undertaken to determine whether prenatal alcohol exposure would result in observable deficits in infant MDI scores. We were particularly interested in examining the effect of different levels of prenatal alcohol exposure on infant mental outcomes, and hypothesized that higher levels would result in greater deficits in infant MDI scores. A linear dose–response effect would be indicated by a gradual increase in the magnitude of the negative effect with increasing doses of prenatal alcohol exposure. In contrast, a threshold effect would be suggested by an effect size close to zero for doses below the threshold, with a significant negative effect at doses beyond the threshold. For example, Abel and Hannigan (1995) found negative effects of alcohol exposure on birth weight at exposure levels greater than two drinks per day, but evidence for a positive association at low levels of exposure. Although some researchers have considered the issue of dose–response versus threshold effects and sought to identify a threshold (e.g. Streissguth *et al*., 1980; Jacobson and Jacobson, 1994), the power to examine this issue is increased by the aggregation of multiple studies in meta-analysis.

METHODS

Literature searches

The MEDLINE database was searched from 1973 through December 2000 for articles involving human subjects that contained the keywords ‘alcohol drinking’ and ‘pregnancy’ (1157 references), the words ‘alcohol drinking’ and ‘prenatal’ (230 references), or the phrase ‘fetal alcohol syndrome’ (1461 references). A comparable search strategy was repeated using the EMBASE and PsycInfo databases as well. This inclusive search strategy was used to avoid missing any relevant studies; however, most references appeared in more than one search. We were able to determine, by the titles and abstracts, that the majority of the articles did not examine the impact of fetal alcohol exposure on infant mental development. Articles whose titles indicated that they potentially might be relevant were examined by two of the authors to determine whether they met the inclusion criteria described below. To further ensure that we included all relevant studies we also consulted the Robert Wood Johnson database, compiled by Barry Lester, and the reference lists from qualitative reviews of the literature and relevant empirical studies. No additional published or unpublished studies that met our inclusion criteria were identified.

Criteria for inclusion/exclusion

To be included in the meta-analysis studies had to: (1) use human subjects 2 years of age or younger; (2) use the MDI from the BSID as the outcome measure; and (3) use a prospective design, in which alcohol usage of mothers was assessed during pregnancy and mental development of resulting offspring was assessed. In several cases, data from the same study were published in more than one article. For example, several papers by the Jacobsons involved separate analyses of the same dataset (Jacobson *et al*., 1993, 1996; Jacobson and Jacobson, 1994, 1999; Kaplan-Estrin *et al*., 1999). Similarly, the sample of Fried and Watkinson (1988) consisted of participants included in an earlier paper (Gusella and Fried, 1984) plus additional subjects. In these cases, effects derived from a given assessment point were included only once in the meta-analysis. A total of nine independent studies met the inclusion criteria; however, as outlined below, we were able to derive multiple effects from these studies. A summary of studies is provided in Table 1.

Table 1. Studies included in the meta-analysis

Reference	*n*	Location	Maternal age (years)	SES/ race	Year of pregnancy	Assessment of alcohol consumption	Age of child at assessment (months)
Coles *et al*. (1987)	60	Atlanta	M = 26	Low/ 92% Black	1981–1984	Intake into prenatal care[a] late in pregnancy	6
Greene *et al*. (1991)	297	Cleveland	M = 22	Low/ 50% White	early 1980s	Average of all prenatal visits[a], retrospective	6, 12, 24
Richardson *et al*. (1995)	561	Pittsburgh	M = 23	Low/49% White	1983–1986	First[a], second, third trimester	8, 18
Streissguth *et al*. (1980)	462	Seattle	M = 26	Middle/ 87% White	1974–1975	Before pregnancy recognition[a], fifth month of pregnancy	8
Jacobson *et al*. (1993)	382	Detroit	M = 26.5	Low/ 100% Black	1986–1989	Average of all prenatal visits[a] at time of conception	12
Kaplan-Estrin *et al*. (1999)	92						26
Fried and Watkinson (1988)	217	Ottawa, Canada	M = 29	Middle/ White?	1978–1983	Average of first, second, third trimester[a]	2, 24
	153						
Parry and Ogston (1992)	247	Odense, Denmark	40% > 29	Middle/ White?	1988–1989	Early pregnancy[a]	18
Parry and Ogston (1992)	522	Berlin, Germany	32% > 29	Middle/ White?	Late 1980s	Early pregnancy[a]	18
Parry and Ogston (1992)	592	Dundee, Scotland	7% > 29	Middle/ White?	1985–1986	Early pregnancy[a]	18

M, mean; *n*, number of sujects; SES, socioeconomic status.
[a]Assessment used for primary analyses.

Effect sizes calculated

Meta-analytical statistics were calculated using the framework for meta-analysis developed by Hedges and Olkin (1985) and used in many other published meta-analytical reviews (e.g. Ito *et al*., 1996; Quigley and Collins, 1999). Overall estimates of effect size are first calculated, followed by analyses of subgroups of effects in order to identify variables that may impact or moderate the relationship between the variables of interest. All effect sizes and homogeneity statistics were calculated using DSTAT meta-analytical software (Johnson, 1989). The effect size calculated was Cohen's *d*, weighted by sample size. A negative *d* indicates that the MDI score was lower among children whose mothers consumed alcohol than among children whose mothers did not consume alcohol while pregnant. For each effect, we also calculated the Pearson correlation coefficient, which reflects the relationship between alcohol exposure (coded dichotomously as 'yes' or 'no') and child MDI score. In order to examine the impact of level of fetal alcohol exposure as a moderator, a between-group homogeneity statistic (Q_b) was calculated and the relationship of alcohol exposure to MDI was examined within three different levels of alcohol exposure. Q_b is analogous to an omnibus *F* statistic and, if significant, indicates differences among categories of the moderator variable. In the present analysis, a significant between-group homogeneity statistics would indicate that the effects of prenatal alcohol exposure on cognitive development differ depending on dosage. We also examined the correlation between mean dosage and effect size.

To examine whether the level of prenatal alcohol exposure influences the degree of mental impairment, we compared effect sizes corresponding to different prenatal alcohol dosages. Given that the majority of pregnant women consume little or no alcohol during pregnancy (Serdula *et al*., 1991), children whose mothers abstained during pregnancy were used as the reference group. Effect sizes were calculated comparing MDI scores of children whose mothers abstained during pregnancy with MDI scores of children whose mothers: (1) consumed an average of less than 1 drink a day during pregnancy (low consumption); (2) consumed an average of 1–1.99 drinks a day (moderate consumption); and (3) consumed an average of 2 or more drinks a day (heavy consumption). As shown in Table 1, the time at which maternal drinking was assessed varied considerably across studies, ranging from time of conception (Streissguth *et al*., 1980) to an average of all prenatal visits (Greene *et al*., 1991; Jacobson *et al*., 1993). Although timing of drinking during pregnancy may have an impact on infant outcome, we were limited to the available data. Two studies provided results based on both first trimester and third trimester maternal drinking (Coles *et al*., 1987; Richardson *et al*., 1995). For the Coles *et al*. (1987) study, the third trimester comparison group consisted of the abstaining group combined with women who had stopped drinking by the third trimester. Primary analyses used first trimester data from these studies; however, results were unchanged when we repeated analyses at 6–8 months and 18–26 months substituting data derived from third trimester drinking.

For studies in which infants of abstaining mothers were compared with infants of mothers at several different levels of consumption (e.g. Streissguth *et al*., 1980; Jacobson *et al*., 1993; Richardson *et al*., 1995) we were able to calculate multiple effects. This allowed an effect size to be estimated for comparisons of different levels of consumption, resulting in stronger meta-analytical tests for moderating effects. If, rather than comparing different conditions within studies, one collapses over variable levels and extracts only a single effect from each study, theoretically important findings may be obscured (Bangert-Drowns, 1986). Although independence of effect sizes is an assumption of meta-analysis (Hedges and Olkin, 1985), if one assumes that the scores of participants in one condition did not influence the scores of participants in other conditions, multiple independent effect sizes can be retrieved from individual studies. A total of 49 independent effect sizes were calculated in this manner (see Table 2). We were able to extract data corresponding to multiple dosage levels from all of the studies except two. Both effects derived from the Coles *et al*. (1987) study were classified as heavy, based upon the mean alcohol consumption in early pregnancy for both groups. Greene *et al*. (1991) provided only a single unadjusted correlation coefficient derived from the sample as a whole. We were unable to obtain additional original data from the authors. Greene *et al*. (1991) did provide means adjusted for covariates for separate dosage levels, allowing us to calculate three separate adjusted effects. Consequently, the unadjusted analysis at 12 months includes seven effects, whereas the adjusted analysis includes nine effects.

Results for children ages 6–8, 12–13 and 18–26 months were analysed separately for several reasons. First, because the Bayley Scales are designed to assess acquisition of age-appropriate developmental skills, MDI assessments differ at these ages. For practical reasons, analysing data separately according to child age at assessment allowed us to use multiple data points from individual studies that followed children over time (e.g. Fried and Watkinson, 1988; Greene *et al*., 1991; Richardson *et al*., 1995). Secondly, analysing data separately for these three age groups also allowed us to examine whether the effects of prenatal exposure are more likely to be apparent during certain developmental stages. Finally, combining data from observations at different ages would violate the necessity for independence of effects, since several studies observed the same children at more than one age.

RESULTS

Effects at 6 months of age

Eleven effect sizes were calculated using the guidelines described above. As shown in Table 3, the overall mean effect size weighted by sample size was not significantly different from zero {d = –0.07 [95% confidence interval (CI) –0.16, +0.02], r = –0.03}, indicating no overall effect of mother's drinking on the MDI score in children at 6 months of age.

Alcohol dosage effects. To examine possible dosage effects, we first correlated the midpoint or mean dosage for each effect with the corresponding effect size. Although there was a significant negative correlation (r = –0.66, $P < 0.05$), the scatterplot of these data points revealed little association between dosage and effect size with the exception of one outlying data point with a very large negative effect size (see Fig. 1). This data point was derived from the heaviest drinking group in the Streissguth *et al*. (1980) study, which consisted of

Table 2. Effects calculated in age analysis

Study effect	SES	*n* (alcohol)	*n* (control)	Drinks per day	Consumption	MDI (alcohol)	MDI (control)	*r*	*d*	(95% CI)
6–8 Months										
Coles *et al.* (1987)[a]	Low	22	27	M = 3.48	Heavy	102.9	111	–0.20	–0.41	–0.98, +0.16
Coles *et al.* (1987)[a]	Low	11	27	M = 4.04	Heavy	113.1	111	+0.07	+0.13	–0.57, +0.83
Greene *et al.* (1991)[b]	Low	297		M = 0.14	Low	112.3		–0.08	–0.15	–0.32, +0.01
Richardson *et al.* (1995)	Low	148	186	0 –0.4	Low	123.5	121.8	+0.04	+0.09	–0.13, +0.30
Richardson *et al.* (1995)	Low	87	186	0.4–1	Low	120.9	121.8	–0.03	–0.05	–0.31, +0.20
Richardson *et al.* (1995)	Low	93	186	> 1	Moderate	124.6	121.8	+0.07	+0.15	–0.10, +0.40
Streissguth *et al.* (1980)[c]	Middle	149	216	0.2–1.98	Moderate	116	116	+0.00	+0.00	–0.21, +0.21
Streissguth *et al.* (1980)[c]	Middle	72	216	2–3.8	Heavy	116	116	+0.00	+0.00	–0.27, +0.27
Streissguth *et al.* (1980)[c]	Middle	13	216	4–5.8	Heavy	116	116	+0.00	+0.00	–0.56, +0.56
Streissguth *et al.* (1980)[c]	Middle	2	216	6–7.8	Heavy	116	116	+0.00	+0.00	–1.39, +1.39
Streissguth *et al.* (1980)[c]	Middle	10	216	8–50	Heavy	98	116	–0.47	–1.06	–1.70, –0.42
12–13 Months										
Fried and Watkinson (1988)	Middle	10	116	> 1.7	Moderate	98.4	109.5	–0.34	–0.72	–1.37, –0.07
Greene *et al* (1991)[b]	Low	279		M = 0.14	Low	111.9		–0.06	–0.11	–0.28, +0.05
Jacobson *et al.* (1993)	Low	233	60	< 0.01–0.5	Low	109.9	113.4	–0.13	–0.27	–0.55, +0.02
Jacobson *et al.* (1993)	Low	37	60	0.5–0.99	Low	107.2	113.4	–0.24	–0.48	–0.90, –0.07
Jacobson *et al.* (1993)	Low	26	60	1.00–1.99	Moderate	105.9	113.4	–0.29	–0.59	–1.06, –0.12
Jacobson *et al.* (1993)	Low	13	60	2–3.99	Heavy	103.2	113.4	–0.37	–0.79	–1.40, –0.17
Jacobson *et al.* (1993)	Low	6	60	> 4	Heavy	100.8	113.4	–0.46	–1.02	–1.88, –0.16
12–13 Months adjusted for covariates										
Fried and Watkinson (1988)[b]	Middle	217		> 1.7	Moderate	108.1		–0.06	–0.12	–0.31, +0.07
Greene *et al.* (1991)[d]	Low	139	93	> 0–0.2	Low	112	111	+0.04	+0.09	–0.17, +0.35
Greene *et al.* (1991)[d]	Low	40	93	0.2–1	Low	112.5	111	+0.07	+0.15	–0.23, +0.52
Greene *et al.* (1991)[d]	Low	7	93	> 1	Moderate	113	111	+0.10	+0.19	–0.57, +0.96
Jacobson *et al.* (1993)	Low	233	60	< 0.01–0.5	Low	109.4	112.7	–0.14	–0.28	–0.56, +0.00
Jacobson *et al.* (1993)	Low	37	60	0.5–0.99	Low	109.4	112.7	–0.13	–0.27	–0.68, +0.15
Jacobson *et al.* (1993)	Low	26	60	1–1.99	Moderate	107.2	112.7	–0.21	–0.43	–0.89, +0.04
Jacobson *et al.* (1993)	Low	13	60	2–3.99	Heavy	106.2	112.7	–0.24	–0.50	–1.10, +0.11
Jacobson *et al.* (1993)	Low	6	60	> 4	Heavy	105.2	112.7	–0.29	–0.60	–1.45, +0.24
18–26 Months										
Fried and Watkinson (1988)	Middle	8	71	> 1.7	Moderate	110.7	119.5	–0.20	–0.41	–1.14, +0.33
Greene *et al.* (1991)[b]	Low	275		M = 0.14	Low	102.4		–0.10	–0.19	–0.36, –0.03
Kaplan-Estrin *et al.* (1999)[e]	Low	48	18	< 0.01–0.5	Low	86.2	90.9	–0.17	–0.35	–0.89, +0.20
Kaplan-Estrin *et al.* (1999)[e]	Low	11	18	0.5–0.99	Low	88.4	90.9	–0.09	–0.17	–0.92, +0.58

Table 2. continued

Study effect	SES	*n* (alcohol)	*n* (control)	Drinks per day	Consumption	MDI (alcohol)	MDI (control)	*r*	*d*	(95% CI)
Kaplan-Estrin *et al.* (1999)[e]	Low	2	18	> 4	Heavy	79.7	90.9	–0.32	–0.64	–2.11, +0.84
Richardson *et al.* (1995)	Low	171	195	0.0–0.4	Low	108.2	107.4	+0.02	+0.05	–0.16, +0.25
Richardson *et al.* (1995)	Low	97	195	0.4–1	Low	111.5	107.4	+0.12	+0.24	–0.00, +0.49
Richardson *et al.* (1995)	Low	98	195	> 1	Moderate	108.5	107.4	+0.03	+0.07	–0.18, +0.31
Parry and Ogston (1992)[f]	Middle	240	257	< 1	Low	107	105	+0.07	+0.13	–0.04, +0.31
Parry and Ogston (1992)[f]	Middle	55	257	< 1	Low	107	105	+0.07	+0.13	–0.16, +0.42
Parry and Ogston (1992)[f]	Middle	19	257	< 1	Low	105	105	+0.00	+0.00	–0.47, +0.47
Parry and Ogston (1992)[f]	Middle	9	257	>1	Moderate	102	105	–0.10	–0.20	–0.86, +0.47
Parry and Ogston (1992)[f]	Middle	12	257	>1	Moderate	99	105	–0.20	–0.40	–0.98, +0.18
Parry and Ogston (1992)[g]	Middle	82	51	< 1	Low	106	107	–0.03	–0.07	–0.42, +0.28
Parry and Ogston (1992)[g]	Middle	52	51	< 1	Low	102	107	–0.17	–0.33	–0.72, +0.06
Parry and Ogston (1992)[g]	Middle	38	51	< 1	Low	102	107	–0.17	–0.33	–0.76, +0.09
Parry and Ogston (1992)[g]	Middle	10	51	> 1	Moderate	105	107	–0.07	–0.13	–0.81, +0.55
Parry and Ogston (1992)[g]	Middle	4	51	> 1	Moderate	109	107	+0.07	+0.13	–0.89, +1.15
Parry and Ogston (1992)[h]	Middle	230	179	< 1	Low	103	98	+0.17	+0.34	+0.14, +0.53
Parry and Ogston (1992)[h]	Middle	79	179	< 1	Low	105	98	+0.23	+0.48	+0.20, +0.75
Parry and Ogston (1992)[h]	Middle	16	179	< 1	Low	104	98	+0.20	+0.40	–0.11, +0.91
Parry and Ogston (1992)[h]	Middle	18	179	> 1	Moderate	110	98	+0.38	+0.82	+0.33, +1.31
Parry and Ogston (1992)[h]	Middle	7	179	> 1	Moderate	99	98	+0.03	+0.07	–0.69, +0.82

SES, socioeconomic status; MDI, Mental Development Index; *r*, Pearson correlation; *d*, effect size.

[a]Coles' study involved two groups of women consuming 2+ drinks per day early in pregnancy. The first effect is derived from a group who continued drinking throughout pregnancy, the second from a group that later stopped drinking.

[b]Effect sizes calculated based on standardized regression coefficient not group means.

[c]Means, SDs, and cell sizes were derived from Rosett and Weiner's (1984) reanalysis of Streissguth's data.

[d]Means and SDs were estimated based upon figures provided in the article.

[e]Data from the same subjects included in Jacobson *et al.* (1993).

[f]Sample from Dundee, Scotland.

[g]Sample from Odense, Denmark.

[h]Sample from Berlin, Germany.

Table 3. Summary of dosage effects by age group

	No. of effects	Cohen's *d*	95% CI	*r*
Effects at 6–8 months				
Low dose (< 1 drink/day)	3	–0.05	–0.17, +0.07	–0.03
Moderate (1–1.99 drinks/day)	2	–0.05	–0.24, +0.14	–0.02
Heavy dose (2+ drinks/day)	6	–0.14	–0.34, +0.06	–0.06
Total	11	–0.07	–0.16, +0.02	–0.03
Effects at 12–13 months				
Low dose (< 1 drink/day)	3	–0.19*	–0.32, –0.05	–0.09
Moderate (1–1.99 drinks/day)	2	–0.64*	–1.02, –0.26	–0.30
Heavy dose (2+ drinks/day)	2	–0.87*	–1.36, –0.37	–0.40
Total	7	–0.28*	–0.40, –0.15	–0.14
Effects at 12–13 months (adjusted for covariates)				
Low dose (< 1 drink/day)	4	–0.07	–0.23, +0.09	–0.03
Moderate (1–1.99 drinks/day)	3	–0.15	–0.32, +0.25	–0.07
Heavy dose (2+ drinks/day)	2	–0.53*	–1.02, –0.04	–0.25
Total	9	–0.13*	–0.24, –0.01	–0.06
Effects at 18–26 months				
Low dose (< 1 drink/day)	14	+0.07**	+0.01, +0.14	+0.04
Moderate (1–1.99 drinks/day)	9	+0.06	–0.11, +0.22	+0.03
Heavy dose (2+ drinks/day)	2	–0.39	–1.21, +0.44	–0.19
Total	25	+0.07	0.00, +0.13	+0.03

d, effect size.
*Significant negative effect indicating lower MDI scores associated with alcohol exposure.
**Significant positive effect indicated higher MDI scores associated with alcohol exposure.

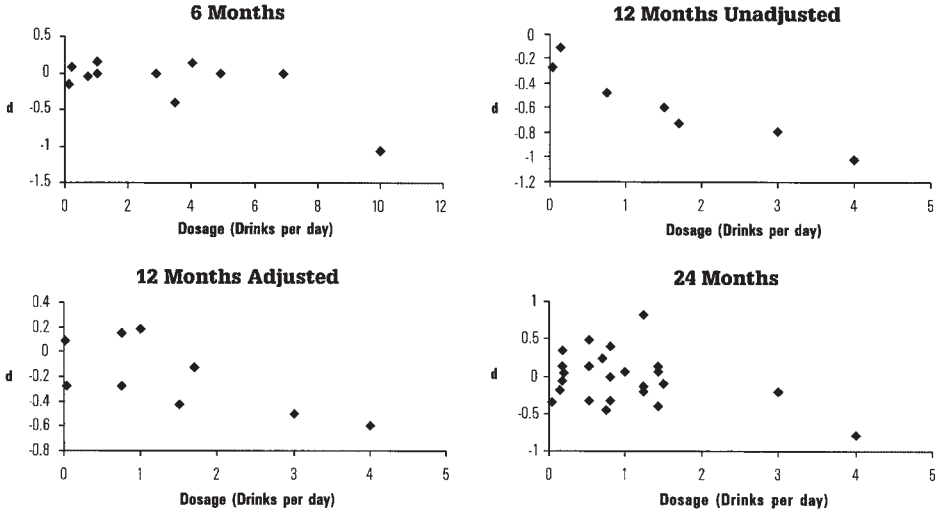

Fig. 1. Dosage by effect size (d) scatterplots for 6-month-old, 12-month-old, and 24-month-old children.

10 women who drank an average of 8–50 drinks per day. When this effect size was removed, the correlation was not significant ($r = –0.06$, $P > 0.10$).

To examine the impact of dosage in more detail, we examined the mean effects for the three separate dosage groups (see Table 3). This analysis controls for sample size by weighting more heavily effects derived from larger samples. The 95% CI for the mean effect of consuming two or more drinks a day included zero, although the effect was in the hypothesized direction [$d = –0.14$ (95% CI –0.34, +0.06), $r = –0.06$]. Likewise, the effects of exposure to moderate (1–1.99 drinks per day) and low (less than 1 drink per day) doses of alcohol were not significant [$d = –0.05$ (95% CI –0.24, +0.14), $r = –0.02$ and $d = –0.05$ (95% CI –0.17, +0.07), $r = –0.03$, respectively]. Consistent with these findings, the between-group heterogeneity statistic did not reach significance [$Q_b(2) = 0.65$, $P = 0.72$].

Effects at 12 months of age

Seven effect sizes were calculated using the guidelines described above (see Table 3). The overall mean effect size weighted by sample size was significantly different than zero [$d = –0.28$ (95% CI –0.40, –0.15), $r = –0.14$], indicating an overall effect of mother's drinking on the MDI score in children at 12 months of age. This translates into a 4.48 point average decrement in MDI scores (95% CI –6.40, –2.40 points) for children whose mothers consumed alcohol during pregnancy.

Alcohol dosage effects. The correlation between mean dose and corresponding effect size was highly significant at 12–13 months of age ($r = –0.95$, $P < 0.05$) (see Fig. 1). We then examined separately effects corresponding to low, moderate and heavy fetal alcohol exposure. The between-group heterogeneity statistic was significant [$Q_b(2) = 10.43$, $P < 0.01$]. There was a significant effect of prenatal exposure of more than 2 drinks per day [$d = –0.87$ (CI –1.36, –0.37), $r = – 0.40$]. This translates to a 13.92-point average decrement in MDI scores (95% CI –21.76, –6.40 points), or nearly a full standard deviation, among infants exposed to 2 or more drinks per day during gestation. There were also significant negative effects on MDI for children exposed to 1–1.99 drinks per day [$d = –0.64$ (95% CI –1.02, –0.26), $r = –0.30$], and for children exposed to less than 1 drink per day [$d = –0.19$ (95% CI –0.32, –0.05), $r = –0.09$].

12-Month findings adjusted for covariates. Because prenatal alcohol use, particularly heavy use, is associated with variables believed to have a negative effect on fetal outcomes (e.g. maternal smoking, drug use, education), experts have advised controlling for these confounding variables (see, for example, Jacobson and Jacobson, 2001). Three studies of 12–13-month-olds provided both unadjusted means or regression coefficients as well as means or coefficients that controlled for the effects of relevant covariates (Fried and Watkinson, 1988; Greene *et al*., 1991; Jacobson *et al*., 1993). For 6–8- and 18–26-month-old children, we did not have sufficient data to conduct analyses using adjusted means. However, for 12–13-month-olds we were able to conduct parallel analyses using means adjusted for various covariates. Covariates differed across studies, because in all three studies selection of covariates was determined empirically (see Table 4). Using the guidelines described above, nine effect sizes adjusted for covariates were calculated (see Table 3). The overall mean effect size weighted by sample size, though quite modest, was significantly different from zero [$d = –0.13$ (95% CI –0.24, –0.01), $r = –0.06$], indicating an overall effect of mother's drinking on the MDI score in children at 12–13 months of age, after controlling for relevant covariates. This translates into a 2.02-point average decrement in MDI scores (95% CI –3.84, –0.16 points).

Using effect sizes adjusted for covariates, we also conducted analyses separately for the three dosage levels. Although the between-group heterogeneity statistic was not significant [$Q_b(2) = 3.18$, $P = 0.20$], examination of the mean effects for each category revealed that the highest exposure level was associated with MDI deficits [$d = –0.53$ (CI –1.02, –0.04), $r = –0.25$]. Thus, after controlling for relevant covariates, there was an average decrement in MDI scores of 8.32 points (95% CI –16.32, –0.64 points), or about half of a standard deviation, among children whose mothers consumed 2 or more drinks per day during pregnancy. The effect of alcohol exposure of 1–1.99 drinks a day was not significant [$d = –0.15$ (95% CI –0.32, +0.025), $r = –0.07$], nor was the effect of exposure to less than 1 drink per day [$d = –0.07$ (95% CI –0.23, +0.09), $r = –0.03$]. The correlation between the midpoint or mean dosage for each effect with the corresponding effect size revealed a significant correlation ($r = –0.69$, $P < 0.05$) (see Fig. 1).

Effects at 18–26 months of age

Twenty-five effect sizes were calculated using the guidelines described above (see Table 3). The overall mean effect size weighted by sample size was not significant [$d = +0.07$ (95% CI +0.00, +0.13), $r = 0.03$].

Alcohol dosage effects. To examine possible dosage effects we first correlated the midpoint or mean dosage for each effect with the corresponding effect size. At 18–26 months of age there was a significant negative correlation ($r = –0.57$, $P < 0.05$). However, examination of the scatterplot (see Fig. 1) suggests, similar to the 6 month data, that this apparent linear effect is the result of two extreme scores. Removing these data points, derived from groups consisting of five women who drank 2–3.99 drinks per day and two women who drank 4 or more drinks per day (Kaplan-Estrin *et al*., 1999), resulted in a non-significant correlation ($r = –0.08$, $P > 0.10$).

We then tested for a possible threshold effect using effects from three separate dosage groups (see Table 3). There was homogeneity among the three dosage levels [$Q_b(2)= 1.21$, $P = 0.54$]. At the low-dosage level, there was a significant effect in the opposite direction from what was predicted [$d = +0.07$ (95% CI +0.01, +0.14), $r = 0.04$]. At the moderate dosage level (1–1.99 drinks per day), the effect of fetal alcohol exposure was not significant [$d = +0.06$ (95% CI –0.11, +0.22), $r = 0.03$]. At the high-dosage level, the effect was in the expected direction [$d = –0.39$, however, the confidence interval included zero (95% CI –1.21, +0.44), $r = –0.19$].

North American versus European studies

The positive relationship between alcohol exposure and MDI among children exposed to less than 1 drink per day was unexpected and appeared to result from the European studies (Parry and Ogston, 1992; see Table 2). We re-examined the relationship between alcohol exposure and MDI for the low-dosage group separately for North American and European studies. Meta-analysis of the five low-dosage effects derived from North American studies revealed a non-significant effect of prenatal exposure to less than 1 drink per day [$d = –0.05$ (95% CI –0.16, +0.07), $r = –0.02$]. In contrast, the nine low-dose effects derived from European studies revealed a significant positive effect [$d = +0.16$ (95% CI +0.06, +0.25), $r = 0.08$].

Table 4. Covariates used in calculating adjusted effects of alcohol on 12–13-month-old children

Study	Covariates
Fried and Watkinson (1988)	Parity, birth weight, gestational age, smoking during pregnancy
Greene *et al*. (1991)	Parity, birth weight, HOME, race, inventory child's gender, number of older siblings, maternal IQ, parental education, mother's pre-pregnancy weight
Jacobson *et al*. (1993)	Maternal age, prenatal visits, smoking during pregnancy, opiates during pregnancy, HOME inventory, maternal depression, child's age at testing, examiner

HOME, Home Observation for the Measurement of the Environment; IQ, intelligence quotient.

There also were six effects involving moderate alcohol exposure derived from European studies. Meta-analysis of these effects revealed a non-significant effect of alcohol on MDI [$d = +0.12$ (95% CI –0.15, +0.38), $r = 0.06$]. Overall, the 15 effects derived from European studies, all involving low or moderate dosage, had an effect in the direction opposite to that predicted [$d = +0.15$ (95% CI +0.06, +0.24), $r = 0.07$]. We also correlated the midpoint or mean dosage for each effect with the corresponding effect size for all 15 effects derived from European studies. The resulting correlation was in the predicted direction but was not significant ($r = –0.12$, $P > 0.05$).

DISCUSSION

Results of this meta-analysis revealed several patterns not readily apparent without quantitative review of the literature. First, the effects of fetal alcohol exposure on infant mental development differed substantially according to infant age at the time of assessment. In observations of 12–13-month-old infants, there was a significant, negative linear effect on MDI. Greater deficits were associated with greater exposure; however, significant negative effects were apparent even at the lowest level of exposure. The negative effect of fetal alcohol exposure among this age group was reduced, but not eliminated, when relevant covariates were included in the calculation of the effects. Despite the significant effects observed among 12–13-month-old children, fetal alcohol exposure was not associated with lower MDI scores among 6–8- or 18–24-month-old children, although at the very highest levels of exposure the few available effects suggested a possible negative impact.

The inconsistency of findings across different age groups may reflect differences in MDI item content at different ages. Item content at 6 months focuses on motor abilities and social interaction, whereas item content at 12 months emphasizes visual perception, spatial relations, short-term memory and attention, and receptive language. Although some visual perception and spatial relation items are still included at 18 months, the test is weighted toward expressive language. The effects of fetal alcohol exposure may have emerged at 12 months of age because the MDI assessment at that age emphasizes abilities that appear to be sensitive to prenatal exposure, such as attention and short-term memory (Mattson and Riley, 1999; Berman and Hannigan, 2000). Abilities assessed at earlier and later ages, such as expressive language, appear less sensitive to alcohol effects (e.g. Fried and Watkinson, 1988; Greene *et al*., 1991). Thus, our pattern of findings may reflect not so much a difference according to age, but according to outcome measure.

Another explanation for the variability in findings across age groups may stem from the general decline in MDI scores that occurs over time among children of low socioeconomic status, regardless of alcohol exposure (e.g. Greene *et al*., 1991; Richardson *et al*, 1995; Kaplan-Estrin *et al*., 1999). This suggests that environmental effects may compound over time, rendering the impact of prenatal alcohol exposure relatively more difficult to detect among such samples. In contrast, among Fried and Watkinson's (1988) middle class sample, MDI scores actually increased from 12 to 24 months, and the impact of prenatal alcohol exposure on MDI, non-significant at 12 months, became significant at 24 months.

Another, perhaps more striking, conclusion that may be drawn from this meta-analytical review is that the body of relevant research is neither as large nor as conclusive as might have been assumed given the large number of qualitative reviews of the literature and the significant impact that the literature has had on social policy and social norms regarding drinking during pregnancy (see Kaskutas, 1995). We were able to identify only nine independent, published, prospective studies that examined the effects of prenatal alcohol exposure on infant mental outcomes. As previously noted, data from some studies were published in multiple articles, leading the casual reader to assume a larger body of literature than is actually the case. Because of the limited number of studies and heterogeneity in measurement, analysis and samples, we urge caution in interpreting results.

We had hoped to shed some light on the nature of the relationship between prenatal alcohol exposure and infant cognitive outcomes; specifically, whether the relationship is better understood as a linear dose–response or a threshold effect. Previous research examining other postnatal outcomes has suggested that the effects of prenatal alcohol exposure may not be detectable at levels less than 2 drinks per day, e.g. birth weight (Abel and Hannigan, 1995) and facial malformations (Polygenis *et al*., 1998). Although negative effects were most pronounced at levels greater than 2 drinks per day among 12–13-month-olds, findings at this age group are consistent with a linear effect. Although the effects of prenatal alcohol exposure were not significant for either 6–8- or 18–26-month-old children, a few effects at high-dosage levels suggest that the heavy exposure may result in lower MDI scores. Unfortunately, there were few effects involving high consumption levels and these effects involved comparison of very small groups of heavy drinking women with large control groups, and consequently, a reduction in statistical power (Hsu, 1993). A failure to recognize that these findings are based on very small numbers of observations can result in distortion of the true pattern of results. For example, although the correlations between dosage and effect size at 6–8 and 18–24 months appeared negative and linear, these correlations were actually the result of very large negative effect sizes derived from tiny samples consisting of 10 (6–8-month data; Streissguth *et al*., 1980), five and two heavy drinking women (18–24-month data; Kaplan-Estrin *et al*., 1999). Both correlations disappeared after removing these effects.

This meta-analysis highlights the need for additional research in this area. In particular, we suggest three important issues for consideration in future studies. First, global measures of infant development such as the BSID may not be sufficient to detect subtle or specific effects of prenatal alcohol exposure. As we have suggested, our finding of significant effects at 12 months but not at younger or older ages, is consistent with the notion that some infant outcome measures are more sensitive to fetal alcohol effects than others. Use of measures that assess specific aspects of infant development (e.g. visual information processing, attentional abilities, numerical reasoning) and are more predictive of later outcomes, may be more useful in determining the impact of alcohol on brain development. Studies using such measures are relatively few in number (for exceptions see Boyd *et al*., 1991; Brown *et al*., 1991; Jacobson *et al*., 1993) and too heterogeneous in terms of outcome measures and child ages to be submitted to meta-analysis. However, it

may be more productive to focus future research efforts on the specific effects of alcohol exposure, rather than continue to rely on global measures such as the MDI to assess fetal alcohol effects.

Secondly, experts in teratology have emphasized the importance of considering relevant covariates in examining the effects of prenatal exposure, since women who use substances in pregnancy are distinguished by a host of other risk factors (Neuspiel, 1994; Day, 1995; Jacobson and Jacobson, 2001). Meta-analysis of 12-month results using effects adjusted for various covariates revealed that although the negative effect of alcohol exposure on MDI remained, the magnitude of this effect was, not surprisingly, reduced compared with the effect using unadjusted means. Unfortunately, the lack of consistency in the covariates used across studies precludes drawing conclusions about the relative importance of alcohol exposure. We suggest that future studies should consider the use of covariates judiciously, using theoretical, *a priori* selection rather than *post hoc* empirical selection. When examining infant cognitive outcomes, it is particularly important to consider the impact of postnatal maternal substance use and the care-giving environment, variables that with few recent exceptions (Eiden *et al*., 1999; Bard *et al*., 2000) have rarely been considered.

Finally, it is important for future research to consider the potential impact of drinking pattern during pregnancy (e.g. moderate regular consumption versus binging) rather than continuing to rely on categorizations of prenatal exposure based on average weekly consumption. Animal studies suggest that the same quantity of alcohol may result in more harm to offspring when consumed all at once than when consumed in smaller, more frequent doses (e.g. Bonthius and West, 1990). Consistent with this finding, Jacobson and Jacobson (1999) found that among mothers who drank at least seven drinks per week ($n = 47$), functionally significant mental deficits (including low MDI scores) were more likely to be observed in infants whose mothers consumed more, than in infants whose mothers consumed fewer, than five drinks per occasion. The differences in the pattern of results observed for European samples versus North American samples may also reflect differences in drinking pattern. Among European mothers, who are believed to consume alcohol in smaller, more frequent doses and with meals, particularly in central and southern Europe (Abel, 1998), the effects of alcohol consumption on infant MDI were null or positive (Parry and Ogston, 1992). The timing of alcohol exposure is related to the issue of dosing. Additional data are needed to determine whether drinking early versus later in pregnancy has a greater impact on fetal outcomes. The data of Coles *et al*. (1987) suggest that continuous heavy drinking throughout pregnancy is associated with lower infant MDI scores, whereas infants whose mothers drink heavily early in pregnancy but stop do not exhibit these deficits. However, Streissguth *et al*. (1980) found stronger negative effects for drinking at the time of conception than for drinking in the fifth month of pregnancy. Given the great practical and theoretical importance of the effects of drinking pattern and timing of drinking, we urge researchers to consider these issues in future studies.

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