Gross Motor Deficits in Children Prenatally Exposed to Alcohol: A Meta-analysis

abstract

BACKGROUND AND OBJECTIVES: Gross motor (GM) deficits are often reported in children with prenatal alcohol exposure (PAE), but their prevalence and the domains affected are not clear. The objective of this review was to characterize GM impairment in children with a diagnosis of fetal alcohol spectrum disorder (FASD) or “moderate” to “heavy” maternal alcohol intake.

METHODS: A systematic review with meta-analysis was conducted. Medline, Embase, Allied and Complementary Medicine Database, Cumulative Index to Nursing and Allied Health Literature, PsycINFO, PEDro, and Google Scholar databases were searched. Published observational studies including children aged 0 to ≤18 years with (1) an FASD diagnosis or moderate to heavy PAE, or a mother with confirmed alcohol dependency or binge drinking during pregnancy, and (2) GM outcomes obtained by using a standardized assessment tool. Data were extracted regarding participants, exposure, diagnosis, and outcomes by using a standardized protocol. Methodological quality was evaluated by using Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

RESULTS: The search recovered 2881 articles of which 14 met the systematic review inclusion criteria. The subjects’ mean age ranged from 3 days to 13 years. Study limitations included failure to report cutoffs for impairment, nonstandardized reporting of PAE, and small sample sizes. The meta-analysis pooled results (n = 10) revealed a significant association between a diagnosis of FASD or moderate to heavy PAE and GM impairment (odds ratio: 2.9; 95% confidence interval: 2.1–4.0). GM deficits were found in balance, coordination, and ball skills. There was insufficient data to determine prevalence.

CONCLUSIONS: The significant results suggest evaluation of GM proficiency should be a standard component of multidisciplinary FASD diagnostic services. Pediatrics 2014;134:e192–e209

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KEY WORDS: fetal alcohol spectrum disorders, alcohol related neurodevelopmental disorder, alcohol drinking, motor skills, child development

ABBREVIATIONS

CI—confidence interval
CNS—central nervous system
CP—cerebral palsy
FASD—fetal alcohol spectrum disorder
FAS—fetal alcohol syndrome
FM—fine motor
GM—gross motor
GMDS—Griffiths Mental Developmental Scales
OR—odds ratio
PAE—prenatal alcohol exposure

Ms Lucas conceived and designed the study, conducted the literature searches for the systematic review, reviewed articles for inclusion, performed data extraction, reviewed article methodology by using the critical appraisal tool, analyzed the data and contributed toward the interpretation of results and wrote the initial drafts of the manuscript; Dr Latimer conceived and designed the study; analyzed the data and contributed toward the interpretation of results and read, edited, and approved the final manuscript; Dr Pinto performed the meta-analysis and analyzed the data, contributed toward the interpretation of results and read, edited, and approved the final manuscript; Ms Doney analyzed the data, contributed toward the interpretation of results, and read, edited, and approved the final manuscript; Ms Ferreira conducted the literature searches for the systematic review, contributed toward the interpretation of results, and approved the final manuscript; Ms Doney performed the meta-analysis and analyzed the data, contributed toward the interpretation of results and read, edited, and approved the final manuscript; Dr Ferreira conducted the literature searches for the systematic review, contributed toward the interpretation of results, and approved the final manuscript; Ms Doney analyzed the data, contributed toward the interpretation of results, and read, edited, and approved the final manuscript; Dr Ferreira conducted the literature searches for the systematic review, contributed toward the interpretation of results, and approved the final manuscript; Ms Doney analyzed the data, contributed toward the interpretation of results, and read, edited, and approved the final manuscript; (Continued on last page)
Alcohol is a teratogen, and exposure in utero may cause a range of lifelong conditions collectively termed fetal alcohol spectrum disorders (FASDs). FASD is an umbrella term describing a continuum of birth disorders caused by maternal alcohol consumption during pregnancy and includes the diagnoses of fetal alcohol syndrome (FAS), partial FAS, and alcohol-related neurodevelopment disorders. FASDs are characterized by significant cognitive, behavioral, and motor deficits, which often persist into adulthood. Not all children exposed to alcohol in utero will develop an FASD because the damage caused will be dependent on the amount, timing, and frequency of the exposure, as well as the genetic predisposition of the fetus and mother.

The few (active case ascertainment) studies that include all disorders in the FASD spectrum reveal a prevalence of 2% to 5% for school-age children in the United States and some Western European countries. Given the lifetime nature of this disorder, more successful outcomes occur when children are diagnosed early facilitating prompt access to interventions and support. The diagnostic process for FASD includes examination for facial dysmorphology, growth restriction, structural central nervous system (CNS) abnormality, and CNS domains of functional impairment. The majority of FASD diagnostic guidelines recommend the assessment of gross motor (GM) and fine motor (FM) functioning within the examination of CNS domains, using standardized cutoffs for impairment at 2 SD below the population mean.

Impairment of GM skills is often reported in children exposed prenatally to alcohol (prenatal alcohol exposure [PAE]), but its prevalence and the specific domains affected are not clear. GM skills are defined as skills requiring the use of large muscle groups to coordinate movement, such as walking, running, throwing, and maintaining balance. FM skills are defined as skills requiring the use of precise coordinated movements such as writing, buttoning, cutting, or tracing. Differentiating between GM and FM skills is important because management strategies to improve deficits understandably differ. In children, GM skills are an integral part of the motor skill repertoire enabling exploration of the environment, social interaction, and play. GM impairment has been reported in children with an FASD diagnosis, as well as in children who do not meet the criteria for FASD but who were exposed prenatally at “moderate” to “heavy” levels of alcohol. At “low” levels (<10 drinks per week) of PAE, GM impairment has not been established. However, reports of FM deficits in children with low PAE do exist. FM deficits, which may affect GM abilities, include bimanual coordination, reaction time involving complex tasks, timing accuracy, and the generation of isotonic and isometric force. Other structural defects seen in FASD such as camptodactyly, decreased elbow pronation/supination, and clubfoot may also interfere with GM abilities in FASD. Reports of the prevalence of GM impairment in children with FASD are currently limited. There is some evidence to suggest that the impact of PAE on motor skill becomes clearer as children grow older and task demands increase.

Currently there is no high quality evidence to describe the effects of an FASD diagnosis or significant levels of PAE on GM proficiency. Understanding the nature and prevalence of GM impairment subsequent to PAE will inform assessments, establish the needs of children with impairment, and assist in developing strategies to address impairment. It is timely to provide parents, clinicians, teachers, and policy makers with the best available evidence. We therefore systematically reviewed the literature in children 18 years or younger with either a diagnosis of FASD or PAE at moderate to heavy levels to establish the following:

1. The association of GM impairment with exposures and diagnosis,
2. Which GM domains are impaired, and
3. The prevalence of GM impairment in these exposures.

We hypothesize that children exposed to moderate to heavy PAE or children with a diagnosis of FASD will have measurable GM deficits.

METHODS

Design

A systematic review of observational studies with meta-analysis was conducted guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. The study protocol was prospectively registered with PROSPERO (register number CRD42012002492; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002492).

Data Sources and Searches

Electronic data sources were systematically searched from earliest record to the first week of November 2012 by using a highly sensitive search strategy outlined in Supplemental Information Appendix 1. A search was conducted of the following: Medline, Embase, Allied and Complementary Medicine Database, Cumulative Index to Nursing and Allied Health Literature, PsycINFO, PEDro, and Google Scholar. Additional references were found by hand searching the reference lists of relevant studies, conference abstracts, and by approaching experts in the field. Searches were not restricted by language.

Study Selection

One reviewer (Ms Lucas) screened all relevant titles and abstracts of the retrieved publications to exclude irrelevant titles. Three reviewers (Ms Lucas, Ms Lau, and Ms Jones) independently assessed the full reports for eligibility against the inclusion and exclusion criteria (Table 1), using standardized forms.
Data Extraction and Quality Assessment

Three reviewers (Ms Lucas, Ms Lau, and Ms Jones) independently extracted data by using standardized forms. Disagreements were resolved by discussion with a fourth reviewer (Dr Ferreira). From studies meeting eligibility criteria, information was extracted on age, gender, study method, standardized assessment tool, GM outcome, prevalence of GM impairment and statistical analysis including means (final scores or change score), SEs or SDs, and sample sizes. Studies required measurement of GM outcome according to criteria in Table 1. Cases were subjects with an FASD diagnosis or PAE at moderate to heavy levels as defined by study authors. Controls were subjects without FASD, or with low levels of PAE or no PAE as defined by study authors.

The methodological quality of studies was independently assessed by 2 reviewers (Ms Lucas and Ms Dries) by using an 8-point critical appraisal tool shown in Supplemental Information Appendix 2, developed from recommendations by the Strengthening the Reporting of Observational Studies in Epidemiology guidelines23 and a recent systematic review of quality assessment tools for observational studies.24 Disagreements were arbitrated by a third reviewer (Dr Ferreira). Table 2 shows the reviewed domains.

Data Synthesis and Analysis

Mean scores, SD or SE for continuous measures of GM proficiency, and sample size from each group (FASD, PAE, or mixed versus control) were used to calculate the standardized mean difference and 95% confidence intervals (CIs). These were converted to odds ratios (ORs) to express association with exposure with 95% CIs.25 When there was insufficient information in published reports, SDs or SEs were estimated by using methods recommended by the Cochrane Group.26

Meta-analysis

Studies were grouped according to subject exposure (1) FASD diagnosis, (2) moderate to heavy levels of PAE and/or binge drinking, or (3) a mixed group including both 1 and 2), and age range (0 to <2 years, 2 to <5 years, 5 to <10 years, and 10 to ≤18 years). Only 1 GM proficiency measure from each study was included in the meta-analysis. When studies revealed >1 GM outcome, a conservative approach was adopted by including the GM proficiency measure that demonstrated the smaller OR. In follow-up studies with multiple time points, the significantly larger initial sample size was taken as the more conservative measure. When studies used the same cohort, only the study with the most conservative OR was included. In one 3-arm study that revealed separate data for FASD, PAE, and control groups, the sample size for the control group was adjusted by dividing the sample size by 2 according to Cochrane guidelines26 to enable inclusion of both comparisons (FASD versus control and PAE versus control). Pooled effects were calculated for each of the 3 exposure groups, and an overall pooled effect was calculated for all studies. Forest plots were used to visually assess the OR and 95% CI of each study and funnel plots to assess for publication bias.

Analyses were performed by using the Comprehensive Meta-Analysis software, version 2.2.04 (Biostat, Eaglewood, NJ) by using a random effects model. Statistical significance was set at 0.05, and heterogeneity was analyzed by using the I² statistic. The outcomes of studies not reported in the meta-analysis were described individually.

RESULTS

Literature Search

The search identified 2873 studies. Hand searching references from systematic reviews and lists provided by

<table>
<thead>
<tr>
<th>TABLE 2 Critical Appraisal Tool Criterion</th>
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<tr>
<td>Control for bias</td>
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<tr>
<td>1. Defined sample</td>
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<tr>
<td>2. Representative sample</td>
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<tr>
<td>3. Blind outcome rating</td>
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<tr>
<td>Appropriate measurement of variable</td>
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<tr>
<td>4. Methods of assessment (a) face validity</td>
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<td>5. Methods of assessment (b) evidence of</td>
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<tr>
<td>psychometrics</td>
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<tr>
<td>6. Outcome data reported</td>
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<tr>
<td>7. Adequate power calculation</td>
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<tr>
<td>Control for confounding</td>
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<tr>
<td>8. Statistical adjustment: multivariable</td>
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<tr>
<td>regression analysis conducted, with</td>
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<td>adjustment for potentially confounding</td>
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<tr>
<td>factors.</td>
</tr>
<tr>
<td>Each of these criteria was explicitly</td>
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<tr>
<td>judged by using: Yes = criterion clearly</td>
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<tr>
<td>satisfied, No = criterion clearly not</td>
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<tr>
<td>satisfied or unclear if criterion is</td>
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<tr>
<td>satisfied. A quality score (maximum</td>
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<tr>
<td>score = 8) was allocated to each individual study</td>
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experts in the field retrieved a further 8 articles giving a total of 2881. After reading titles and abstracts, 14 articles were included in the systematic review, 10 of these being included in the meta-analysis. All studies found were published in English (Fig 1).

Characteristics of Included Observational Studies
The 14 included studies were categorized into 3 groups: (1) children diagnosed with an FASD \((n = 4)\), (2) children exposed prenatally to alcohol at moderate to heavy levels \((n = 5)\) or binge drinking \((n = 1)\), or (3) children with a mix of 1 and 2 \((n = 4)\). The mixed group included 2 studies of children with mothers with confirmed alcohol dependency. The age of subjects within the studies ranged from 3 days to 13.1 years. There were no studies for the 2 to <5 age group in the meta-analysis. Table 3 summarizes the characteristics of these studies and the prevalence of GM impairment. Table 4 relates GM proficiency outcomes with exposure.

Authors’ Definitions of PAE
Of the studies included in the systematic review, there were 7 where authors stated that subjects had been exposed to PAE at moderate to heavy or “high” levels, and 2 where mothers were alcoholics. Authors defined moderate ranging from 2 to \(\geq 14\) drinks per week, and heavy from \(>10\) to 28 drinks per week. “Binge drinking” was defined as \(\geq 5\) drinks at one occasion. Timing of PAE with respect to gestation was mentioned in 3 of 6 studies and was variable. Two authors defined a standard drink as 12 g of alcohol and one as 14 g of \(>10\) to 28 drinks per week. Studies excluded from this systematic review on the basis of low PAE had exposures lower than these classifications.

Risk of Bias and Assessment of Quality
Quality of included studies is presented in Table 5. The 8 quality criteria were chosen to provide evidence of careful study design and psychometrics. The total quality score ranged from 4 to 8 of a possible score of 8. The majority of studies \((12 of 14)\) scored 5 or higher. The most common methodological flaw was omission of a power calculation to interpret clinical significance \((10 of 14)\). Rater blinding was absent in half the studies \((7 of 14)\); however, 5 of these studies involved children diagnosed with an FASD and it is acknowledged that it may not be possible to blind assessors regarding the child’s physical features. Four studies did not adjust for confounding variables. Few articles revealed psychometrics \((8 of 14)\), but in reviewing the standardized assessment tools it is likely that only 1 study used a tool that was not validated.

Publication bias of the meta-analysis was assessed by using a funnel plot (Supplemental Information Appendix 3), which revealed the presence of slight asymmetry. This may be attributed to some small study effects as our search retrieved more studies with small sample sizes less than 100 \((8 of 10)\), and most of these studies had subjects with FASD, which were more likely to show GM impairment.

Outcome Measures
Of the 14 studies in the systematic review, 10 different assessment tools were used to measure GM performance (Table 4). Five studies revealed the profession of the rater performing the GM assessments: psychologists \((n = 2)\), physiotherapists \((n = 2)\), or either occupational therapists or physiotherapists \((n = 1)\).

Effects of Prenatal Alcohol Exposure on GM Performance
Data were pooled from 10 of the 14 included studies in a meta-analysis. Data for the meta-analysis are shown in Supplemental Information Appendix 4.

Studies Included in the Meta-analysis

(1) GM Performance in Subjects Diagnosed With FASD
Meta-analysis: Five observational studies were pooled in the FASD diagnosis group (Fig 2). The age of children in these studies ranged from 7 months to 13.1 years. Pooled results revealed an FASD diagnosis was associated with GM impairment \((OR: 3.0; 95\% CI: 2.0–4.4)\), random effects meta-analysis, \(I^2 = 0\%\).

Individual Studies: Of 2 studies that used the Griffiths Mental Developmental Scales (GMDS) locomotion subscale, one revealed GM impairment \((OR: 3.8; 95\% CI: 2.1–6.5)\) among 7- to 12-month-old infants, whereas the other study revealed none in children with mean age 7 years \((OR: 1.9; 95\% CI: 0.8–4.5)\). GM impairment was also reported in a ball skills subscale among children with mean age 8.8 years \((OR: 2.7; 95\% CI: 1.1–6.5)\) and a static balance subscale \((OR: 4.5; 95\% CI: 0.9–23.7)\) in children with mean age 11.9 years, but not in an upper limb “reaction time with movement” task involving children with mean age 13.1 years \((OR: 2.4; 95\% CI: 0.6–10.0)\).

(2) GM Performance in Subjects With Moderate to Heavy or Binge Drinking Levels of PAE
Meta-analysis: Three observational studies were pooled in the moderate to heavy or binge drinking levels of PAE group (Fig 2). The age of children in these studies ranged from 3 days to 13.1 years. Pooled results reveal that PAE at these levels was not significantly associated with GM impairment \((OR: 1.1; 95\% CI: 0.4–2.7)\), random effects meta-analysis, \(I^2 = 5\%\).

Individual Studies: GM impairment (ie, general tonus, maturity, pull-to-sit, defensive movements, activity OR: 2.7; 95% CI: 1.2–6.5) were detected in 3-day-old infants with PAE across 3 trimesters by using the Brazelton Neonatal Behavioral Assessment Screen. GM impairments,
however, were not found in children with mean age 5.2 years in a GM sub-area based on ball skills (OR: 0.8; 95% CI: 0.4–1.4), who were exposed to isolated episodes of binge drinking (maximum 3+ episodes) over the first 8 weeks of trimester 1, nor in an upper limb "reaction time and movement to a target" task for children of mean age 13.1 years (OR: 0.6; 95% CI: 0.2–1.7).

(3) GM Performance in Mixed Exposure Group (ie, Subjects With FASD and Moderate to Heavy or Binge Drinking Levels of PAE)

Meta-Analysis: Three observational studies were pooled in the mixed group (Fig 2). The age of children ranged from 18 months to 12.1 years. Pooled results reveal that alcohol exposure is associated with GM impairment (OR: 4.9; 95% CI: 2.4–10.2, random effects meta-analysis, I² = 0%).

Individual Studies: One study assessed 18- to 19-month-old toddlers with PAE across 3 trimesters and revealed 30.8% of subjects presented with significant delay in attaining independent walking (OR: 4.4; 95% CI: 1.4–13.5). The second study revealed impaired coordination in children with mean age 5.4 years whose...
TABLE 3  Systematic Review: Individual Study Characteristics (n = 14)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Population Source</th>
<th>Mean Age (SD, when provided)</th>
<th>Total No. of Subjects (Case and Control Group)</th>
<th>Assessor’s Profession</th>
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<tr>
<td><strong>FASD diagnosis (n = 4)</strong></td>
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<tr>
<td>Age range, 0 – &lt;2 y</td>
<td>Cohort with control group</td>
<td>Recruited subjects were born between 2002 and 2003 in the public hospital at De Aar, South Africa.</td>
<td>(1) Not reported; 7–12 mo; (2) Not reported: 17–21 mo</td>
<td>(1) n = 392; (2) n = 83</td>
<td>Not reported</td>
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<tr>
<td>Davies et al 201136,a</td>
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<tr>
<td>Age range, 5 – &lt;10 y</td>
<td>Cohort with matched control group</td>
<td>Exposed subjects were recruited from Grade 1 classes in Cape Town, South Africa. Reference group subjects were selected from the above sample whose mothers did not admit to moderate or heavy drinking during pregnancy.</td>
<td>Cohort: 7.0 (0.5) y; Control: 7.1 (0.5) y</td>
<td>n = 68</td>
<td>Not reported</td>
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<td>Adnams et al 200128,a</td>
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<tr>
<td>Kooistra et al 200932,a</td>
<td>Cohort with control group</td>
<td>ADHD subjects were recruited from 2 private schools and 1 clinic specializing in learning and attention problems. FASD subjects were recruited through the FASD clinic at a regional pediatric hospital. Reference group subjects were recruited from 2 participating elementary schools. All subjects were from the Calgary, Canada region.</td>
<td>Cohort: 8.8 (1.2) y; Control: 9.1 (1.1) y</td>
<td>n = 116</td>
<td>Not reported</td>
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<tr>
<td>Jirikowic et al 201338,a</td>
<td>Cohort with matched control group</td>
<td>Exposed group subjects were recruited from the University of Washington Fetal Alcohol Syndrome Diagnostic and Prevention Network clinical registry and database. Reference group subjects were recruited from a university research participant pool and matched for age and gender.</td>
<td>Cohort: 11.9 (2.5) y; Control: 12.0 (2.5) y</td>
<td>n = 20</td>
<td>Physical therapist or occupational therapist.</td>
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<td><strong>Moderate to heavy alcohol exposure or binge drinking (n = 5)</strong></td>
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<td>Age range, 0 – &lt;2 y</td>
<td>Cohort with control group</td>
<td>Subjects were recruited from Grady Memorial Hospital, Georgia, between January 1981 and September 1983.</td>
<td>Cohort: 3 d; Control: 3 d</td>
<td>n = 149</td>
<td>Psychologist</td>
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<td>Smith et al 198635</td>
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<tr>
<td>Coles et al 198731,a</td>
<td>Cohort with control group</td>
<td>Subjects were recruited from Grady Memorial Hospital, Georgia, between January 1981 and July 1984.</td>
<td>Cohort: 3 d; Control: 3 d</td>
<td>n = 103</td>
<td>Not reported</td>
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<tr>
<td>Age range, 2 – &lt;5 y</td>
<td>Cohort with control group</td>
<td>Subjects were recruited at 2 unspecified study hospitals (Seattle, WA).</td>
<td>Cohort: 4.3 (0.04) y; Control: 4.3 (0.04) y</td>
<td>n = 449</td>
<td>Psychologist</td>
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<tr>
<td>Barr et al 199037</td>
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<td>Age range, 5 – &lt;10 y</td>
<td>Cohort with control group</td>
<td>Subjects were recruited from Danish National Birth Cohort between 1997 and 2003 and form a sample known as the Lifestyle During Pregnancy Study.</td>
<td>Cohort: 5.2 y; Control: 5.2 y</td>
<td>n = 685</td>
<td>Physiotherapist</td>
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<td>Bay et al 201212</td>
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<tr>
<td>Kesmodel et al 201339,a</td>
<td>Cohort with control group</td>
<td>Subjects were recruited from Danish National Birth Cohort between 1997 and 2003 and form a sample known as the Lifestyle During Pregnancy Study.</td>
<td>Cohort: 5.2 y; Control: 5.2 y</td>
<td>n = 678</td>
<td>Physiotherapist</td>
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<tr>
<td><strong>FASD and moderate to heavy alcohol exposure (n = 2)</strong></td>
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<tr>
<td>Age range, 0 – &lt;2 y</td>
<td>Cohort with control group</td>
<td>Subjects were recruited from a special clinic for pregnant women with chronic alcohol abuse at the University Central Hospital, Helsinki, Finland, between 1983 and 1998. Reference group subjects were recruited from volunteer mothers abstinent throughout their pregnancy (n = 19) or the successive births of low risk pregnancies (n = 37). Either source was not reported.</td>
<td>Not reported: 18–19 mo</td>
<td>n = 109</td>
<td>Not reported</td>
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mothers had confirmed alcohol dependency (OR: 4.1; 95% CI: 1.3–13.3). This study also revealed neurologic findings consistent with cerebral palsy (CP). Within this study’s sample of 21 children (including FAS [n = 10]), 1 subject was diagnosed with hemiplegia and a further 14% (6 of 21) of subjects had signs of slight tremor and axial ataxia. It was not reported whether these findings were specifically associated with the FAS subjects. The third study demonstrated impaired balance skills in children with mean age 12.2 years (OR: 9.2; 95% CI: 1.8–47.8).

### (4) Overall Pooled Effect

The overall pooled effect demonstrates an association between a diagnosis of FASD or moderate to heavy maternal alcohol intake and GM impairment (OR: 2.9; 95% CI: 2.1–4.0, random effects meta-analysis, I² = 8%).

**Studies Unable to Be Included in the Meta-analysis**

Two studies were excluded from the moderate to heavy PAE group. One was excluded because it only provided adjusted and not crude regression GM outcomes. It assessed 4-year-old children by using a battery of GM tasks. Balance was significantly impaired and revealed a linear relationship with increasing PAE. Additionally, observed timing and error deficits were not captured by the standardized assessment tool (F = 5.00, P = .026). A second study was excluded because it provided inadequate information on sample size. It revealed nonsignificant findings in 3-day-old infants with PAE over 3 trimesters by using the Brazelton Neonatal Behavioral Assessment Screen (mean: 4.69; SD: 1.05, P > .05). Two additional studies in the mixed group were excluded for revealing the least conservative GM deficits of 2 studies derived from the same cohort. One study revealed impairment in the GMDS locomotor subscale in children aged 1.5 to 9 years of mothers with confirmed alcohol dependence (OR: 21.0; 95% CI: 4.1–106.2). The other revealed nonsignificant findings in children aged 5.2 years in the GM subarea on the basis of ball skills (OR: 0.8; 95% CI: 0.3–2.3).

### Prevalence of GM Impairment

Only 1 study in this systematic review revealed prevalence of GM impairment. Significant delay was observed in 30.8% of subjects aged 18 to 19 months in attaining independent walking by using a cutoff of 1 SD below the mean. This is a common threshold for impairment in many motor assessments and contrasts to the −2 SD used for FASD diagnosis.

Table 6 shows a summary of GM impairment according to OR calculations in the included studies. No study reported structural defects impeding GM abilities.

### DISCUSSION

This is the first known systematic review to define and measure the effect of PAE on GM proficiency. Our meta-analysis findings suggest that in children with an FASD diagnosis or those exposed to moderate to heavy levels of alcohol prenatally, the odds of GM impairment are tripled. Our conclusion is supported by findings of GM impairment in 6 of 10 studies included in the meta-analysis (and 10 of 14 studies included in the systematic review). GM impairment.
TABLE 4 Systematic Review: Association of Alcohol Exposure With GM Performance Outcomes (n = 14)

<table>
<thead>
<tr>
<th>Study</th>
<th>Alcohol Exposure</th>
<th>Reference Group</th>
<th>Standardized Assessment Tool</th>
<th>GM Outcomes</th>
<th>Associations</th>
<th>Confounders and BCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davies et al 2011 (n = 145, FASD); (n = 35, FASD)</td>
<td>(1) n = 45; FASD; (2) n = 35; FASD</td>
<td>(1) n = 347; No FASD, but some PAE; (2) n = 48; No FASD, but some PAE</td>
<td>GMDS&lt;sup&gt;c&lt;/sup&gt; Locomotor subscale</td>
<td>Mean (SD); (1) 7–12 mo; FASD: 89.8 (17.9); Reference group: 100 (13.4); P &lt; .001; GM outcome: impaired; (2) 17–21 mo; FASD: 78.3 (17.8); Reference group: 90.1 (13.4); P &lt; .001; GM outcome: impaired</td>
<td>None reported.</td>
<td>Not matched for BCs.</td>
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<td>Adnams et al 2001 (n = 34; FAS); Mean (SD): 84.1 drinks/wk (13.25); Drinks/wk</td>
<td>n = 34; No FAS, but some PAE exposure: Mean (SD): 303 drinks/wk (5.18); Drinks/wk</td>
<td>GMDS&lt;sup&gt;c&lt;/sup&gt; Locomotor subscale</td>
<td>Mean (SE); PAE group: 102.13 (1.49); Reference group: 104.93 (1.30); F(1,10) = 6.09, P &lt; .001. GM outcome: no impairment</td>
<td>Maternal education.</td>
<td>BCs matched on child's age, gender, first language, family income and school.</td>
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<td>Kooistra et al 2009 (n = 77; FASD (n = 30); ADHD (n = 47); Groups: ADHD–C (combined ADHD group; n = 31), ADHD–PI (predominantly inattentive; n = 16)</td>
<td>n = 39; No ADHD or FASD</td>
<td>M-ABC&lt;sup&gt;d&lt;/sup&gt; Static and dynamic balance subscale; Ball skills subscale</td>
<td>None reported.</td>
<td>BCs matched for gender and SES.</td>
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<td>Jinkovic et al 2013 (n = 10; FASD)</td>
<td>n = 10; Typically developing (&lt; 3 drinks throughout pregnancy)</td>
<td>(1) M-ABC2&lt;sup&gt;e&lt;/sup&gt;; (2) p-CTSIB-2&lt;sup&gt;f&lt;/sup&gt;; (3) DGI&lt;sup&gt;g&lt;/sup&gt; Balance total; Static balance; Dynamic balance</td>
<td>Mean (SD); PAE group: 85.2 (2.7), Reference group: 11.3 (3.1), P = .08; GM outcome: no impairment; Balance; total ordinal score: PAE group: 27.8 (2.9), Reference group: 29.1 (1.1), P = .07; GM outcome: no impairment; Balance; vestibular sensory system score: PAE group: 8.2 (1.4), Reference group: 9.3 (1.1), P = .06; GM outcome: no impairment; PAE group: 21.4 (1.4), Reference group: 23.2 (1.1), P = .02, GM outcome: impaired</td>
<td>Not performed because of small sample size.</td>
<td>BCs matched for age and gender.</td>
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<td>Study</td>
<td>Alcohol Exposure</td>
<td>Reference Group</td>
<td>Standardized Assessment Tool</td>
<td>GM Outcomes</td>
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<td>Smith et al 1986[^35]; PAE level: moderate to heavy alcohol exposure or binge drinking (n = 4) Age range, 0 – &lt;2 y</td>
<td>Moderate to heavy alcohol exposure or binge drinking (n = 4) Age range, 0 – &lt;2 y</td>
<td>n = 149; “Stopped” group 28–56 g (2–4 drinks) in first and second trimesters; “Continued” group: 56–142 g (4–10 drinks) in 3 trimesters; Continued group: 170–388 g (12–26 drinks) in 3 trimesters; Continued group: &gt;386 g (28 drinks) in 3 trimesters; g AA/wk[^h,k]</td>
<td>n[^h]; “Never” group: 0 g; g AA/wk</td>
<td>BNBAS[^i] Motor performance cluster score</td>
<td>Mean (SD); “Never” group: 4.97 (0.99); Stopped group: 4.53 (1.01); Continued groups combined: 4.89 (1.05); P &gt; .05; GM outcome: no impairment</td>
<td>Smoking for growth parameters only. Not matched for BCs.</td>
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<tr>
<td>Coles et al 1987[^31,a]; PAE level: “high risk”</td>
<td>n = 48; Stopped group: 345 g (12 drinks) in first and second trimesters (n = 22); Continued group: 345 g (12 drinks) in first through third trimesters (n = 26); g AA/wk[^h]</td>
<td>n = 55; Never group: 0 g; g AA/wk</td>
<td>BNBAS[^i] Motor Performance cluster score</td>
<td>Mean (SD); Never group: 4.96 (0.98); Stopped group: 4.66 (1.13); Continued group: 4.40 (1.06); F (1,99) = 3.07; P &lt; .05; GM outcome: Continued group differed significantly to Never group in motor performance (ie, general tonus, maturity, pull-to-sit, defensive movements, activity).</td>
<td>None reported. Not matched for BCs.</td>
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<tr>
<td>Barr et al 1989[^27]; PAE level: moderate to high; 10 oz AA = 2 standard drinks</td>
<td>n = 449; At least 0.5–1.5 oz (at least 7 to ≥21 drinks/wk[^f]); oz AA/wk</td>
<td>n[^h]; Abstainers[^h,j]; oz AA/wk</td>
<td>“Battery of gross motor tasks”[^l] based on: (1) GMTOT; (2) The Gesell; (3) BSID – PD; Items tested were balance, coordination, and distance subscales</td>
<td>Balance, coordination, and distance subscales</td>
<td>Mean (SD); Balance: 76 (8); Coordination: 55 (15); Distance: 47 (18); R = 0.27, F = 5.00; P = .026; GM outcome: Increasing alcohol exposure in early pregnancy was related to increasing poor balance</td>
<td>Caffeine, nicotine, aspirin, gender; birth order; maternal race age, and prenatal nutrition, maternal and paternal education, examiner, and age of child. Not matched for BCs.</td>
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Age range, 5 – <10 y
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<tr>
<th>Study</th>
<th>Alcohol Exposure</th>
<th>Reference Group</th>
<th>Standardized Assessment Tool</th>
<th>GM Outcomes</th>
<th>Associations</th>
<th>Confounders and BCs</th>
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<tr>
<td>Bay et al 2012&lt;sup&gt;12&lt;/sup&gt;; PAE level: only moderate PAE included for this review</td>
<td>n = 93; (1) 5–8 drinks/wk (n = 82); (2) ≥9 drinks/wk (n = 11); Drinks/wk</td>
<td>n = 325; 0 drinks/wk; Drinks/wk</td>
<td>M-ABC&lt;sup&gt;4&lt;/sup&gt;</td>
<td>GM subarea: catching beanbag, rolling ball; Balance subarea: one-leg balance, jumping over cord, walking heels raised.</td>
<td>Mean difference (95% CI); (1) PAE group: −0.41 (−1.31 to 0.48), P = .79; GM outcome: no impairment; (2) PAE group: −0.40 (−2.18 to 1.39), P = .79; GM outcome: no impairment; (1) PAE group: −0.66 (−1.74 to 0.42), P = .47; GM outcome: no impairment; (2) PAE group: 1.06 (−1.78 to 3.88), P = .47; GM outcome: no impairment</td>
<td>Parental education, maternal IQ, prenatal maternal smoking, maternal age, parity, maternal binge drinking episodes during pregnancy, prenatal and postnatal marital status, postnatal parental smoking, maternal prepregnancy BMI, child gender, age at testing, health status, hearing and vision on the day of testing, family/home environment, and physical activity (organized sport). Not matched for BCs.</td>
</tr>
<tr>
<td>Kesmodel et al 2013&lt;sup&gt;59,60&lt;/sup&gt;; PAE level: Binge drinking defined as an intake ≥5 standard drinks on a single occasion; 1 standard drink = 12 g AA</td>
<td>n = 160; 3+ binges; Binge drinking episodes over the first 8 wk in first trimester</td>
<td>n = 48; 0 binges; Binge drinking episodes over the first 8 wk in first trimester</td>
<td>M-ABC&lt;sup&gt;4&lt;/sup&gt;</td>
<td>GM subarea: catching beanbag, rolling ball. Balance subarea: one-leg balance, jumping over cord, walking heels raised.</td>
<td>Mean difference (95% CI); PAE group: −0.32 (−1.09 to 0.49), P = .78; GM outcome: no impairment; PAE group: 0.42 (−0.85 to 1.68), P = .42; GM outcome: no impairment</td>
<td>Parental education, maternal IQ, prenatal maternal smoking, prenatal maternal average alcohol intake, maternal age, parity, prenatal and postnatal marital status, postnatal parental smoking, maternal prepregnancy BMI, child gender, age at testing, health status, hearing and vision on the day of testing, family/home environment, and physical activity (organized sport). Not matched for BCs.</td>
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Mixed: FASD and moderate to heavy alcohol exposure (n = 5)
Age range, 0 – <2 y
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<tr>
<th>Study</th>
<th>Alcohol Exposure</th>
<th>Reference Group</th>
<th>Standardized Assessment Tool</th>
<th>GM Outcomes</th>
<th>Associations</th>
<th>Confounders and BCs</th>
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<tr>
<td>Autti-Rämö and Granström 1991</td>
<td>n = 53; (1) &gt;28–140 g (2–10 drinks) in first trimester (n = 21); (2) &gt;140 g (10–45 drinks) in first and second trimesters (n = 19; inclusive of 1 FAS child); g AA/day; (3) &gt;140 g (10–45 drinks) (n = 19), AA/wk in first – third trimesters, (n = 13; inclusive of 5 FAS children); g AA/week</td>
<td>n = 56; 0 g (0 drinks); g AA/day</td>
<td>GMTOT&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Age of independent walking (months)</td>
<td>Mean (P value, pairwise analysis with no PAE); No PAE 11.97, Group 1: 12.48, P &gt; .05; Group 2: 13.45, P &lt; .05&lt;sup&gt;31&lt;/sup&gt;; Group 3: 14.23, P &lt; .01&lt;sup&gt;32&lt;/sup&gt;; F = 5.93 (3), P = .0009 (difference between all groups); GM outcome: Significantly delayed independent walking in groups 2 and 3</td>
<td>None reported. Not matched for BCs. (Higher level of 2-parent families in controls, and higher foster families/children's homes in groups 2 and 3).</td>
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<tr>
<td>Age range, 5 – &lt;10 y Aronson et al 1985&lt;sup&gt;20&lt;/sup&gt;</td>
<td>n = 21; Children of alcohol-dependent mothers (n = 20; inclusive of 10 FAS children)</td>
<td>n = 21; PAE&lt;sup&gt;5&lt;/sup&gt; (Only n = 13 case control pairs for GMDS for children &lt;7 y of age)</td>
<td>GMDS&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Locomotor subscale</td>
<td>Mean (SD); PAE group: 95.7 (12); Reference group: 113.5 (9), P &lt; .001; GM outcome: impaired</td>
<td>None reported. BCs matched for gender, age, BW, GA, and living area but not for smoking.</td>
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<tr>
<td>Kyllerman et al 1985&lt;sup&gt;33&lt;/sup&gt;</td>
<td>n = 21; Children of alcohol-dependant mothers (n = 20; inclusive of 10 FAS children)</td>
<td>n = 21; PAE&lt;sup&gt;6&lt;/sup&gt;</td>
<td>CTS&lt;sup&gt;7&lt;/sup&gt; based on the Oseretsky Test of Motor Proficiency</td>
<td>Coordination</td>
<td>Mean (SD); (2) CTS; PAE group 2.2 (1.1), Reference group 3.1 (1.2), P &lt; .05; GM outcome: impaired</td>
<td>None reported. BCs matched for gender, age, BW, GA, and living area but not for smoking.</td>
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<tr>
<td>Age range, 10 – &lt;18 y Roebuck et al 1998&lt;sup&gt;34&lt;/sup&gt;; PAE level: heavy</td>
<td>n = 11; FAS (n = 8); Heavy&lt;sup&gt;8&lt;/sup&gt; PAE (n = 3)</td>
<td>n = 11; Minimal exposure&lt;sup&gt;9&lt;/sup&gt;</td>
<td>SOT&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Equilibrium composite score</td>
<td>Mean (SE); PAE group: 70.73 ± 2.84; Reference group: 78.64 ± 1.27, F(1,17) = 18.77, P &lt; .01; GM outcome: balance impaired when somatosensory input was inaccurate</td>
<td>None reported. BCs matched on age and gender</td>
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<tr>
<td>Study</td>
<td>Alcohol Exposure</td>
<td>Reference Group</td>
<td>Standardized Assessment Tool</td>
<td>GM Outcomes</td>
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<td>Simmons et al 2010[^37]</td>
<td>PAE level: heavy</td>
<td>n = 28; FAS (n = 9), heavy PAE (n = 19); Heavy = 3–4 glasses of wine/day, being drunk day and night, drinking a fifth of vodka or case of beer each day</td>
<td>Response box with multifunction timing device[^*], standardized procedures</td>
<td>Reaction time alone (milliseconds); Reaction time and move (milliseconds); Movement time (milliseconds)</td>
<td>Mean (SE): FAS: 437.9 ms (46.9), PAE: 378.2 ms (22.0), Control: 378.6 (88), F (2,49) = 2.87, P &gt; .05; GM outcome: no impairment; FAS: 612.9 ms (70.4), PAE: 493.5 ms (19.9), Control: 467.2 (62.4), F (2,49) = 6.15, P &lt; .05; GM outcome: FAS group slower reaction time. Target 1: FAS: 505.7 ms (43.1), PAE: 375.9 ms (29.8), Control: 364.4 ms (27.7), F (2,49) = 4.13, P &lt; .05; GM outcome: Slower movement times to targets in FAS children. Significantly longer and more variable reaction times in FAS children. Significant results repeated for Target 2 and 3. Target 2: FAS: 857.4 ms (68.6), PAE: 595.5 ms (47.4), Control: 661.3 ms (44.1), F (2,49) = 4.99, P &lt; .01; Target 3: FAS: 1171.2 ms (89.5), PAE: 862.8 ms (61.8), Control: 913.9 ms (57.8), F (2,49) = 4.22, P &lt; .05.</td>
<td>None reported. Not matched for BCs.</td>
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<tr>
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<td>n = 23; No PAE</td>
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[^37]: Studies included in meta-analysis.
[^*]: PAE not quantified.
[^*]: Higher scores indicate better performance.
[^*]: Lower scores indicating better performance.
[^*]: Higher score indicates better performance.
[^*]: Higher scores indicate better performance.
[^*]: Higher scores indicate better performance.
[^*]: Subjects per group not provided.
[^*]: Higher scores indicate better performance.
[^*]: Ounces AA converted to grams AA for comparison purposes (1 ounce = 28.35 g).
[^*]: Grams AA converted to drinks for comparison purposes (1 standard drink = 14 g AA US definition).
[^*]: Battery of gross motor tasks: higher scores indicate better performance.
[^*]: Higher scores indicate better performance.
[^*]: Prevalence of GM impairment = 31.6%.
[^*]: Prevalence of GM impairment = 30.8%.
[^*]: Higher scores indicate better performance.
[^*]: Lower scores indicate better performance.
[^*]: Response box with multifunction timing device: lower scores indicate better performance.
impairment was consistently found regardless of assessment tool employed, in subjects with mean age from 3 days to 13.1 years by using only the most conservative estimates from each of the studies. We demonstrated a higher pooled impairment effect in children with an FASD diagnosis (group 1; OR: 3.0 [95% CI: 2.0–4.1]) compared with the moderate to heavy or binge drinking PAE exposure (group 2; OR: 1.1 [95% CI: 0.4–2.7]). It is unclear from the studies whether children with an FASD diagnosis were exposed to greater levels of alcohol in utero than those with heavy to moderate exposure.

The nonsignificant impairment after moderate to heavy or binge drinking exposure was unexpected in the meta-analysis. Close inspection of the studies suggests the small numbers of studies (n = 3), sensitivity of tasks to detect GM impairment,27 young age (3 days),31 and other factors affecting the degree of expression of alcohol-related birth disorders, such as dose, pattern, and timing of PAE,2,3 may have contributed to this outcome. The nonsignificant impairment in the binge-drinking group was expected. Despite the binge exposures occurring over at a critical period of brain development (3 to 6 weeks’ gestational age),41 70%, 21%, and 9% of participants had 1, 2, and 3+ binge drinking episodes, respectively, during the 8 weeks of this study. Taken together this binge drinking study39 may represent lower PAE exposures. The highest association in the meta-analysis was found in the mixed group (group 3; OR: 4.9 [95% CI: 2.4–10.2]). It is likely that the tasks assessed in group 3 may actually be more sensitive to impairment than those in groups 1 and 2. Furthermore, this result may have been strengthened by the high proportion of subjects with FASD (approximately 50%).

Five studies in the meta-analysis and 1 study excluded used assessment tools revealing impairment in specific domains of GM proficiency almost always sensitive to impairment than those in groups 1 and 2. Furthermore, this result may have been strengthened by the high proportion of subjects with FASD (approximately 50%).

The slight asymmetry of the funnel plot most likely reflects the higher number of small studies with positive outcomes (GM impairment) conducted in patients with a higher risk of publication bias although the low power of these plots limits the conclusions that can be obtained.42 Sources of publication bias may be derived from location bias (eg, only English published studies were found) or selective outcome reporting (eg, exclusion of studies not providing GM outcomes) or small-study effects (eg, higher OR estimates in small compared with large FASD studies).

This meta-analysis has 4 key strengths. First, we used a prospective protocol and highly sensitive search strategy including hand searching of conference proceedings to locate the best available evidence to reduce bias. We used a funnel plot to investigate publication bias although the low power of these plots limits the conclusions that can be obtained.42 Sources of publication bias may be derived from location bias (eg, only English published studies were found) or selective outcome reporting (eg, exclusion of studies not providing GM outcomes) or small-study effects (eg, higher OR estimates in small compared with large FASD studies).

The slight asymmetry of the funnel plot most likely reflects the higher number of small studies with positive outcomes (GM impairment) conducted in patients with a higher risk of publication bias although the low power of these plots limits the conclusions that can be obtained.42 Sources of publication bias may be derived from location bias (eg, only English published studies were found) or selective outcome reporting (eg, exclusion of studies not providing GM outcomes) or small-study effects (eg, higher OR estimates in small compared with large FASD studies).
each of the studies hence the reported pooled effects are the most conservative estimates. Fourth, bearing in mind the small study base, the included studies were conducted in diverse settings including the United States \((n = 6)\), Europe \((n = 5)\), Africa \((n = 2)\), and Canada \((n = 1)\), suggesting that the finding of GM impairment is not geographically specific. The results of this systematic review are generalizable to populations with low and higher socioeconomic status and a variety of racial backgrounds.

There are several limitations in the current literature that impact the conclusions from our meta-analysis. First, most of the studies \((8\text{ of }10)\) had small sample sizes \(<100\) subjects, which may reflect challenges in finding and recruiting subjects affected by PAE. Small studies increase the risk of type 2 error such that small GM deficits that may be present may not be detected. Second, the cutoff used to determine GM impairment was only reported in 2 studies, which may be a source of heterogeneity when combining studies. Third, sources of bias may be derived from the omission of power calculations \((7\text{ of }10)\), but this is negated by the relatively precise CIs of most of the OR calculations (Fig 2). Fourth, 4 of 10 studies did not adjust for confounders, which means there is the potential to wrongly attribute GM deficits to PAE when other factors may be contributing. Importantly, the results of this meta-analysis provide evidence of association and not causation. Fifth, confounding, selection bias, and heterogeneity are key sources of error in the meta-analysis of observational studies. We acknowledge that the quality of the data available to be extracted will limit the interpretation of the pooled effect. This includes the risk of parents underestimating the amount of alcohol consumed prenatally and the author attributing GM deficits to a lesser exposure than what actually occurred. Sixth, there were inconsistencies reporting PAE across the studies because there is no gold standard for collecting information on alcohol exposure. In this review, we used the study authors’ definitions of low, moderate, and heavy PAE. We identified 1 study containing subjects with lower PAE \((2\text{ to }4\text{ drinks per week})\). This study was not included in our meta-analysis because it provided insufficient data from which measures of association could be calculated. Finally, the assessment tools
used to detect GM impairment may not have been sufficiently sensitive to capture GM impairment.\textsuperscript{28} The size of the overall pooled OR may have been greater if the methodological design related to these last 2 points were improved.

Two previous systematic reviews focused on the effect of PAE on balance and the threshold of PAE for GM impairment, but meta-analysis was not undertaken. The first review investigated the effect of any level of PAE on balance.\textsuperscript{47} Only 1 of the 4 included studies was considered to have robust methodology and was the only study that revealed an association with PAE and impairment in balance-related outcomes at undisclosed moderate levels of PAE. The second review investigated the threshold for motor impairment specific to PAE, finding high daily alcohol intake (>10 drinks per week) is associated with deficits in GM and FM function, whereas the effects associated with binge drinking are uncertain.\textsuperscript{11} Other studies have also revealed the link in children with PAE to motor presentations consistent with CP\textsuperscript{33,48,49} This aligns with reports that heavy maternal alcohol consumption is a direct cause of prenatally and an indirect cause of postnatally acquired CP\textsuperscript{50} indicating the link to PAE should be considered in some cases of CP diagnosis.

This review highlights challenges in the accurate measurement of GM impairment in children with PAE particularly when using assessments that combine a battery of tasks and generate scores where it is not possible to distinguish between GM and FM abilities (eg, Bayley Scales of Infant Development, Psychomotor Development Index\textsuperscript{51}). A total of 14 articles were excluded from this review for this reason.\textsuperscript{19,48,52} GM impairment may also be underestimated by tools that lack sensitivity such as the broad GMDS locomotor sub-scale\textsuperscript{28,36,64} or do not include components of timing and speed.\textsuperscript{20,33} In this review, we chose to include only standardized tools to reduce measurement bias; however, some experimental laboratory based assessments may also capture specific elements of GM impairment (eg, reaction time).

This review also highlights the challenges of classifying PAE. Differences were reported across the individual studies with respect to definitions of dose, pattern, and timing of PAE and alcoholic content of a standard drink. There were 3 studies\textsuperscript{30,31,35} that classified subjects according to timing of PAE across all 3 trimesters. Two of these studies\textsuperscript{30,31} revealed a trend of worsening GM impairment with PAE across all trimesters. Recommendations for future studies include improving study design and removing sources of heterogeneity.\textsuperscript{41} We propose the use of age appropriate

\begin{table}[h]
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\caption{Systematic Review: Summary of GM Impairment According to OR Calculations}
\begin{tabular}{|l|l|l|l|l|l|l|l|l|l|l|}
\hline
Reference & Balance & GMDS \textsuperscript{-Locomotion Subscale} & BNBAS Cluster Scores & Coordination Ball Skills & Delayed Independent Walking & Reaction Time & Reaction Time and Move & CP \\
\hline
FASD & Davies et al 2011\textsuperscript{36} & Yes GMDS & No GMDS & & & & & \\
 & Adnams et al 2004\textsuperscript{28} & Yes GMDS & No GMDS & & & & & \\
 & Kooistra et al 2009\textsuperscript{32} & M-ABC\textsuperscript{c} & No BNBAS & Yes M-ABC & & & & \\
 & Jirikowic et al 2013\textsuperscript{34} & Yes DGI, p-CTSIB-2\textsuperscript{c}, M-ABC2 & No M-ABC & No M-ABC & & & & \\

Moderate to heavy PAE & Smith et al 1986\textsuperscript{35} & No BNBAS & & & & & & \\
 & Coles et al 1987\textsuperscript{37} & Yes BNBAS & & & & & & \\
 & Bay et al 2012\textsuperscript{12} & No M-ABC & No M-ABC & & & & & \\
 & Kesmodel et al 2013\textsuperscript{39} & No M-ABC & No M-ABC & & & & & \\
 & Autti-Rämö and Granström 1991\textsuperscript{30} & GM Battery\textsuperscript{b} & & & & & & \\
 & Barr et al 1999\textsuperscript{37} & Yes GMTOT & & & & & & \\

Mixed exposure & Aronson et al 1985\textsuperscript{29} & Yes GMDS & Yes CTS & & & & & \\
 & Kyllerman et al 1985\textsuperscript{33} & & & & & & & \\
 & Roebuck et al 1998\textsuperscript{44} & Yes SOT & & & & & & \\
 & Simmons et al 2010\textsuperscript{27} & No RB & & & & & & \\

\hline
\end{tabular}
\textsuperscript{a} GM impairment reported by authors but excluded from OR calculations as least conservative GM deficit.
\textsuperscript{b} GM impairment reported by authors but excluded from OR calculations as crude data not provided.
\textsuperscript{c} GM impairment reported by authors but not by OR calculations.

\end{table}
assessment tools to inform diagnostic processes and evidenced-based intervention plans that are sensitive, clinically robust, capture functional difficulties, and reveal outcomes relative to SD cutoffs. Guidelines for age appropriate assessment tools are provided within some international diagnostic criteria.67,68 The cutoff for GM impairment within the more rigorous international FASD diagnostic processes is 2 SD below the mean (< third centile).1,6 We suggest a second cutoff of 1 SD below the mean (<16th percentile) could be used to designate the need for treatment of GM difficulties and is the cutoff commonly set in many standardized assessments for this.43,66,67 Future studies researching GM impairment should consider classifying PAE by using a standardized instrument that includes assessment of dose, pattern, timing, and definition of a standard drink to establish risk of fetal harm and timing of alcohol exposure in relation to GM deficits. Larger prospective cohort studies are needed to ascertain the development of GM impairment over time and its expression at different ages. Additional improvements in GM assessment could be provided by using physiotherapists rather than psychologists to perform the GM assessment, because physiotherapists are highly skilled in this and able to provide therapeutic interventions. PAE may damage both central68–70 and peripheral nervous system structures71–73 resulting in a range of GM impairments. This meta-analysis demonstrated GM impairment in the domains of balance, coordination, and ball skills, which underpin many fundamental skills used on a daily basis by children (eg, running to catch a school bus, balancing to get dressed, playing basketball, and sitting at school). GM impairment may also affect a child’s ability to participate and socialize with peers.67 In the long term, this may result in a sedentary lifestyle74 and an increased risk of chronic disease secondary to physical inactivity.74–76

CONCLUSIONS

This meta-analysis provides evidence of GM impairment in children exposed to significant alcohol prenatally. On the basis of our findings, we recommend that the evaluation of GM proficiency and strategies to ameliorate impairment should be a standard component of FASD diagnostic and management services. Further work is required to develop a standardized approach for assessing GM proficiency in children with maternal alcohol exposure or an FASD.

ACKNOWLEDGMENTS

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