Perinatal infections and neurodevelopmental outcome in very preterm and very low birth weight infants: a meta-analysis

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Abstract

Objective This quantitative meta-analysis summarizes studies evaluating the effect of perinatal infections on neurodevelopmental outcome in very preterm birth/very low birth weight (VLBW) infants.

Data Sources We searched Medline, PsychInfo, EMBASE and Web of Knowledge for studies on infections and neurodevelopmental outcome.

Study Selection All titles and abstracts were assessed for eligibility by two independent reviewers.

Main Exposure Perinatal infections.

Main Outcome Measure Bayley Scales of Infant Development 2nd edition (BSID-II) scores.

Results This meta-analysis includes 18 studies encompassing data on 13,755 very preterm/VLBW infants. Very preterm/VLBW infants with perinatal infections have poorer mental ($d=-0.25$, $p<.001$) and motor development ($d=-0.37$, $p<.001$) compared to very preterm/VLBW infants without infections. Mental development is most impaired by necrotizing enterocolitis (NEC) ($d=-0.40$, $p<.001$) and meningitis ($d=-0.37$ $p<.001$). Motor development is most impaired by NEC ($d=-0.66$ $p<.001$). Chorioamnionitis did not affect mental ($d=-0.05$, $p=.37$) or motor development ($d=0.19$, $p=.08$).

Conclusions Postnatal infections have detrimental effects on mental and motor development in very preterm/VLBW infants.
**Introduction**

Very preterm delivery (≤32 weeks of gestation) and very low birth weight (VLBW, ≤1500 grams) is strongly associated with intrauterine infections, and the majority of very preterm/VLBW infants develop at least one neonatal infection. There is increasing evidence that infections contribute to brain damage which leads to adverse neurodevelopmental outcome in this at-risk population.

Infection and inflammation may contribute to both preterm birth and damage to the developing brain. The local release of inflammatory cytokines, particularly IL-1, IL-6 and TNF-α, could lead to preterm labour through stimulation of prostaglandin release by fetal membranes and uterine deciduas. Furthermore, inflammatory cytokines may directly cause damage to the preterm brain by increasing the permeability of the blood-brain barrier and interfering with normal myelinisation by damaging myelin and myelin producing cells. Very preterm infants with infections are also at increased risk for respiratory and circulatory insufficiency, which further increases the risk for hypoxic and ischemic brain injury. The cytokines which are produced during infections can have a systemic effect causing hypotension and disseminated intravascular coagulation, and therefore indirectly contribute to cerebral brain damage. In recent studies, perinatal infections in preterm infants were related to periventricular leukomalacia and echolucent lesions, reflections of white matter damage (WMD) which are in turn associated with poor outcomes in later life.

This meta-analysis quantitatively aggregates the literature on perinatal infections and neurodevelopmental outcome measured with the Bayley Scales of Infant Development (BSID-II). Results may contribute to identifying infants at risk for adverse neurodevelopmental outcome and targeting these vulnerable infants for interventions to improve outcomes.

**Methods**

**Selection of Studies**

Medline, PsychInfo, EMBASE and Web of Knowledge were searched for studies evaluating the relation between perinatal infections and neurodevelopmental outcome in very preterm and/or VLBW infants. We used the keywords preterm, prematur* and very low birth weight to select studies involving our target population. To search for studies regarding
perinatal infections we used the keywords infection and inflammation with all possible suffixes (e.g., infections, infectious, inflammatory), and the keywords ‘cytokine*’, cytokinemia, bacteriamia, fungemia in British and American orthography. In addition, we searched for all common pre- and neonatal infections, namely urinary tract infection, sepsis, pneumonia, meningitis, necrotizing enterocolitis (NEC), encephalitis, chorioamnionitis, funisitis, candidiasis, villitis and fetal vasculitis. Neurodevelopmental outcome measurement was searched for by the keywords Bayley*, BSID, ‘bayley scales’, neurodevelopment, neuropsycholog*, child development, executive functioning, intelligence, psychomotor, and aptitude test. We used Medical Subject Headings (MeSH) for MEDLINE, thesaurus terms for PsycInfo and EMTREE terms for EMBASE. Furthermore, we screened the reference lists of identified articles to search for additional eligible studies. The search was conducted on December 12th 2011.

The following preselected criteria justified inclusion in this meta-analysis: (1) the study included infants born very preterm (≤32 weeks) and/or with VLBW (≤1500 gr.); (2) the study compared infants with and without perinatal infection; (3) follow-up using BSID-II; (4) results were published in an English-language peer-reviewed journal. We included studies measuring neurodevelopmental outcome with BSID-II. This scale is the most commonly used to measure neurodevelopmental outcome. It consists of a Mental Development Index (MDI), Psychomotor Development Index (PDI), and behavioural rating scale (BRS). Scores on the BSID-II are normalized and have a mean (SD) of 100 (15). Higher scores indicate better neurodevelopment.

All retrieved titles and abstracts were assessed for eligibility by two independent reviewers (EOGvV and JFdK). Duplicate publications found in more than one database were removed. The full text article was retrieved and evaluated if both reviewers considered the abstract potentially relevant. Disagreements were settled by discussion. For full text articles meeting all the preselected inclusion criteria, data were extracted on year of study, sample characteristics, type of infection and BSID-II scores. From studies using the same cohort of participants, the study with the most comprehensive data was included in the meta-analysis.

Quality Assessment

Two authors (EOGvV and JFdK) independently assessed the quality of each included study using the Newcastle-Ottawa Scale. Scores on this instrument range from one to nine,
with higher scores indicating higher quality. Each study was assessed on the quality of the 
selection of participants, (four criteria), comparability of study groups (one criterion), and 
outcome assessment (three criteria). Inconsistencies in ratings were resolved by discussion.

**Statistical Analyses**

Statistical analyses were conducted using Comprehensive Meta-Analysis version 2. 
We contacted authors for additional data if necessary. When only medians were reported, 
techniques by Hozo et al.\textsuperscript{16} were used to estimate means and standard deviations. If means 
and standard deviations were not reported in the article, odds ratios were calculated using 
the available data. Effect sizes for both MDI and PDI (Cohen’s $d$) were determined for each 
study separately. We calculated mean differences for continuous data and odds ratios for 
dichotomous data. Q- and $I^2$-test statistics were conducted to test heterogeneity among the 
studies’ effect sizes. The $I^2$ value is the percentage of variation in effect sizes among studies 
due to heterogeneity rather than due to chance. Values of 25\%, 50\%, and 75\% represent 
respectively low, moderate and high heterogeneity.\textsuperscript{17} The overall effect of infection on both 
the MDI and PDI subscale was computed by weighting each study’s effect size by the study’s 
sample size. We tested if effect sizes were different for studies reporting continuous or 
dichotomous data. In addition, we tested whether the overall effect of infection was similar 
for MDI and PDI scores, i.e. whether infections affect mental and motor development to a 
similar extent. If three or more studies reported on a particular type of infection, the overall 
effect size of this type of infection was calculated. Heterogeneity tests were conducted on 
the overall effect sizes calculated for types of infection to test if all types of infection affect 
Bayley scores to a similar extent. The relationship between study quality score and effect 
size was studied by linear regression analysis.

A major concern in conduction meta-analysis is the possibility of publication bias. We 
therefore investigated the correlation between sample sizes and effect sizes of each study. 
Furthermore, Rosenthal’s fail-safe N (FSN)\textsuperscript{18} was calculated, which measures the necessary 
number of non-significant studies to nullify the overall effect. In addition, we investigated 
the degree of funnel plot asymmetry using linear regression methods proposed by Egger et 
al.\textsuperscript{19}. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 
Statement was followed whenever appropriate.\textsuperscript{20}
Results

We identified 2,573 abstracts using the prespecified search strategy. Data of 18 studies\textsuperscript{4,21-37} were pooled for meta-analysis, encompassing data on 13,755 very preterm/VLBW infants. Details on selection of studies and reasons of exclusion are specified in Figure 1. Nine studies reported Bayley scores on very preterm/VLBW infants with NEC, eight on infants with sepsis, four on infants with meningitis and six studies reported data on infants with chorioamnionitis. No significant association was found between study quality and effect size (β=-0.02, p=.26) or sample size and effect size (β=-0.00001, p=.46). Furthermore, no significant association was found between age at assessment and effect size (β=0.007, p=.42). There was no difference in effect size between studies reporting continuous outcome measures and studies reporting dichotomous outcome measures (Q(1)=0.21, p=.65 for MDI and Q(1)=0.74, p=.39 for PDI). None of the studies reported on behaviour rating scale scores.

Any type of infection – Mental development

BSID-II MDI scores were reported in 17 studies\textsuperscript{4,21,23-37} encompassing a total of 13,649 very preterm/VLBW infants. Seven studies reported data on more than one type of infection. Very preterm/VLBW infants with perinatal infections had significantly poorer MDI scores compared to infants without perinatal infections, as indicated by the combined random effect size of $d=0.25$ (95% confidence interval [CI] 0.14-0.36, p<.001, Figure 2). Only random-effect size could be calculated due to heterogeneously distributed data (Q=89.05, p<.001).

All but five studies\textsuperscript{23,24,32,34,40} reported lower MDI scores in infants with perinatal infections. Four studies\textsuperscript{24,32,34,40} reported no differences in MDI scores between VLBW/very preterm infants with and without perinatal infections. The study of Fung et al.\textsuperscript{23} reported non-significant higher MDI scores in infants with infection. Interestingly, these results became significant in our meta-analysis, most probably because we used parametric statistics in whereas Fung et al. used non-parametric statistics. However, the reported effect size for this study was small ($d=-0.34$) and excluding the study from our analysis did not change the significance of the overall effect size. Analyses were based on 12 studies reporting means and standard deviation, four studies reporting odds values for MDI scores <70, one study reporting odds values for MDI scores <85, and one study reporting odds...
values for MDI scores <55. Excluding the study reporting MDI scores <55 did not change the significance of the overall effect size.

Fail-safe N for the MDI scores was 435, and the Egger degree of funnel plot asymmetry was not significant (p=.22), together indicating no evidence for the presence of any publication bias.

**Any type of infection – Motor development**

BSID-II PDI scores were reported in 11 studies.\(^4,21,22,25-27,29,30,32,33,40\) Meta-analysis of data from these studies encompassing 11,491 very preterm/VLBW infants, indicated that infants with perinatal infections had significantly poorer PDI scores compared to infants without perinatal infections (\(d=0.37\), 95% CI 0.25-0.48, p<.001, Figure 3). The data were
heterogeneously distributed ($Q=37.73$, $p<.001$), therefore a random-effect model was used. Two studies$^{27,32}$ reported no significant difference in PDI scores between infants with and without perinatal infections. Fail-safe $N$ was 342 and the Egger degree of funnel plot asymmetry was not significant ($p=.26$), together indicating that there was no evidence of publication bias. One of the studies reported odds rates for PDI scores $<55$. Excluding this study did not change the significance of the overall effect size.

The overall effect sizes for MDI and PDI scores were significantly different ($Q(1)=9.04$, $p=.003$), indicating that perinatal infections have a greater impact on PDI than on MDI scores in VLBW/very preterm infants.

Figure 2. Meta-analytic outcomes and forest plot of the differences in Mental Developmental Index scores between very preterm children with and without perinatal infections

<table>
<thead>
<tr>
<th>Study</th>
<th>Infection</th>
<th>Cohen’s $d$</th>
<th>Forrest plot of the Mental Developmental Index score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benjamin et al., 2006</td>
<td>Candidemia</td>
<td>0.44</td>
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<tr>
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<tr>
<td>Yeh et al., 2004</td>
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<tr>
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<td>NEC</td>
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<td>Sepsis</td>
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</table>
Growing into a different brain

Nine studies reported MDI scores on NEC, four studies on meningitis, eight studies on sepsis, and five studies reported MDI scores on chorioamnionitis. The combined effect size for NEC was $d=0.40$ (95% CI 0.29-0.51, $p<.001$). The combined effect size for meningitis was $d=0.37$ (95% CI 0.20-0.54, $p<.001$). There was no difference in MDI scores between infants with and without sepsis ($d=0.05$, 95% CI -0.09 to 0.22, $p=.43$) and between infants with and without chorioamnionitis ($d=0.05$, CI 95% -0.06 to 0.17, $p=.37$). Combined effect sizes for the four types of infections differed significantly ($Q(3)=29.42$, $p<.001$). Table 1 depicts the results of post-hoc analysis comparing each type of infection. Mental development was mainly affected by NEC and meningitis.

Five studies reported PDI scores on NEC, five studies on sepsis, and three studies reported PDI scores on chorioamnionitis. Only one study reported PDI scores on meningitis, therefore no combined effect size could be calculated for this type of infection.

![Figure 3. Meta-analytic outcomes and forest plot of the differences in Psychomotor Developmental Index scores between very preterm children with and without perinatal infections.](image-url)
infection. The combined effect size for NEC was $d=0.66$ (95% CI 0.31-1.01, $p<.001$). The combined effect size for sepsis was $d=0.31$ (95% CI 0.18-0.43, $p<.001$). The combined effect size for chorioamnionitis was small and non-significant ($d=0.19$, 95% CI -0.02 to 0.40, $p=.08$), indicating that very preterm/VLBW infants with chorioamnionitis do not have significantly lower PDI scores compared to those without chorioamnionitis. Meta-analytic effect sizes on PDI for the three infection types differed significantly ($Q(2)= 8.06$, $p= .02$). The overall effect size of NEC was significantly higher compared to the combined effect size of sepsis and the combined effect size of chorioamnionitis (Table 1).

<table>
<thead>
<tr>
<th>Infection</th>
<th>Q-value</th>
<th>p</th>
</tr>
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<tr>
<td>MDI NEC vs. Meningitis</td>
<td>0.10</td>
<td>.76</td>
</tr>
<tr>
<td>NEC vs. Sepsis</td>
<td>19.85</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NEC vs. Chorioamnionitis</td>
<td>17.82</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Meningitis vs. Sepsis</td>
<td>8.72</td>
<td>.003</td>
</tr>
<tr>
<td>Meningitis vs. Chorioamnionitis</td>
<td>9.09</td>
<td>.003</td>
</tr>
<tr>
<td>Sepsis vs. Chorioamnionitis</td>
<td>0.21</td>
<td>.65</td>
</tr>
</tbody>
</table>

| PDI NEC vs. Sepsis         | 5.97    | .02   |
| NEC vs. Chorioamnionitis   | 6.15    | .01   |
| Sepsis vs. Chorioamnionitis | 0.73  | .39   |

Note. MDI: Mental Development Index; PDI: Psychomotor Development Index; NEC: Necrotizing Enterocolitis. Bold numbers pertain to a significant p-value ($p<.05$).

**Discussion**

This meta-analysis provides sound evidence for the presence of impairment in mental and motor development among very preterm/VLBW infants with perinatal infections in comparison to very preterm/VLBW infants without infections, with an average decrease in MDI and PDI scores of 0.25 and 0.37 SD, translating into 3.8 and 5.6 points respectively. Mental development is mostly impaired by NEC and meningitis, with a decrease of MDI score of 0.40 SD (6 points) and 0.37 SD (5.6 points) respectively compared to very preterm/VLBW infants without these complications. Motor development is mainly impaired by NEC, with a decrease of PDI score of 0.66 SD (10 points). The reported impact of infections on MDI and PDI scores add up to the well-known detrimental effects of prematurity.
Growing into a different brain

Preterm infants with NEC are often exposed to a suboptimal nutritional condition due to prolonged enteral feed intolerance and dependence on central venous catheters for parenteral nutrition. The need for surgical interventions in NEC may further contribute to poor developmental outcome. In meningitis, a high amount of bacteria circulating in the blood is thought to be necessary for the invasion of the CNS. As a response to brain invasion, leukocytes release factors that contribute to local vasospasm and vasculitis contributing to brain damage.

In this meta-analysis, chorioamnionitis had no effect on mental or motor development. Although chorioamnionitis is unequivocally a risk factor for preterm delivery, studies assessing the effects of intrauterine infections on neurodevelopmental impairment in very preterm/VLBW infants report contradictory results. There are several possible explanations for these contradictory results. Since chorioamnionitis is often associated with lower gestational age and birth weight, the common correction for gestational age may underestimate the actual contribution of chorioamnionitis to developmental outcome. Furthermore, in a cohort of very preterm infants, the control group of very preterm/VLBW infants without intrauterine infection might be exposed to other, possible more devastating events leading to preterm birth. This meta-analysis indicates a higher impact of infection on PDI scores than on MDI scores. A possible explanation is that in particular white matter development and the white matter myelinization process, essential for corticospinal tract functioning and motor behavior, might be vulnerable to the adverse effects of infections. In addition, the thalamic nucleus, especially the reticular nuclei, and basal ganglia are most commonly involved in PVL. These areas are important in voluntary motor control and balance. The higher prevalence of PVL in infants with infections might explain part of the difference in the effect on neurodevelopmental sequelae.

Besides the general associations between infections and neurodevelopmental outcome as described in this meta-analysis, three studies conducted additional analysis on type of micro-organism causing infections. Schlapbach et al. found that Gram-positive sepsis was associated with a fourfold risk of cerebral palsy and a twofold risk of neurodevelopmental impairment compared to uninfected infants. Infants with Gram-negative sepsis had a somewhat increased risk of neurodevelopmental impairment compared to uninfected infants, but this effect decreased after adjustment for confounders.
However, these results should be interpreted with caution since mortality was highest for infants with Gram-negative sepsis. Stoll et al.\textsuperscript{4} found lower MDI and PDI scores among infected infants regardless of pathogen type. Furthermore, Berger et al.\textsuperscript{22} found higher risk of poor PDI scores in infants with Ureaplasma species compared to infants with negative culture results, but did not found significant associations between poor PDI scores and isolation of other pathogens.

This meta-analysis has some limitations that should be taken into consideration. Although the BSID-II is the most widely used instrument to assess neurodevelopment, it does have some restrictions. The BSID-II relies on subjective observations and classifications by examiners for determining mental and motor performance. However, in most studies the tests were administered by experienced examiners who were blinded for medical history, and the inter-rater reliability of this test have been extensively studied and was found satisfactory.\textsuperscript{49} The BSID-II is found to be poor to moderately predictive for neurodevelopmental outcome at school age.\textsuperscript{50,51} Although the validity of standardized mean differences reported in meta-analysis is debatable,\textsuperscript{52} it enables the opportunity to aggregate studies reporting outcomes on continuous and dichotomous scales. Additionally, it should be noted that some effect sizes in this meta-analysis were based on a small number of studies, and should be interpreted with caution. The considerable heterogeneity found in some analysis indicate variability among the studies. Meta-analytic methods are not without limitations, especially when the source of heterogeneity is unclear or when publication bias is present.\textsuperscript{17} Nevertheless, the source of heterogeneity in the outcomes of this meta-analysis was clear: in order to overcome the limitation of small sample sizes that limits most studies into the effects of infections on the outcomes of preterm born infants we summarized studies on the effect of different types of infections. Furthermore, some heterogeneity in definitions of sepsis and chorioamnionitis was present across studies. All studies defined sepsis by a positive blood culture. Besides, some studies used additional clinical signs in their definition. For chorioamnionitis, the majority of studies relied on histological evidence, although some exceptions should be noted: Berger et al.\textsuperscript{22} used positive amnion cultures as a definition of chorioamnionitis. Furthermore, Fung et al.\textsuperscript{23} also included infants with exclusively clinical signs of chorioamnionitis. Excluding this study did not change the meta-analytic effect size and its significance. Besides the effect of infection on brain development and neurodevelopmental outcome, prematurity itself is a risk factor for cerebral pathology.
Growing into a different brain

For example, IVH, PVL and diffuse white matter injury is frequently observed in very preterm born infants. Some studies included in this meta-analysis describe significant associations between infections and brain injuries like intraventricular haemorrhage and white matter disease.\textsuperscript{24,27,30} For example, Berger et al. found more cystic PVL in infants with intrauterine Ureaplasma infection, compared to infants with negative amnion cultures.\textsuperscript{22} Due to small sample size, PVL was not included in the analysis on the effect of neurodevelopmental outcome in that study. McKee et al. found both infection and IVH as a predictor for poor neurodevelopmental outcome.\textsuperscript{26} However, some other studies did not find significant associations between infection and brain damage,\textsuperscript{23} or brain damage and mental development.\textsuperscript{34} Recently, Brochu et al.\textsuperscript{53} found distinctive patterns of neuroinflammatory response on hypoxic-ischemic injury and bacterial endotoxins depending on the stage of brain maturation in rodents. Future studies are warranted to further disentangle the associations between type of infection, brain damage and neurodevelopmental outcome in very preterm/VLBW infants.

Together, the results of this meta-analysis highlight the additional deteriorating effect of infections on neurodevelopment impairments in very preterm/VLBW infants and stresses the clinical importance of the prevention of perinatal infections.

References


Growing into a different brain


