Periventricular/Intraventricular Hemorrhage and Neurodevelopmental Outcomes: A Meta-analysis

Amit Mukerji, MDa, Vibhuti Shah, MDa, Prakesh S. Shah, MDa

abstract

**CONTEXT:** Periventricular/intraventricular hemorrhage (PIVH) is a common short-term morbidity in preterm infants, but its long-term neurodevelopmental impact, particularly with mild PIVH, remains unclear.

**OBJECTIVE:** To systematically review and meta-analyze the neurodevelopmental outcomes of preterm infants ≤34 weeks’ gestation with mild and severe PIVH, compared with no PIVH.

**DATA SOURCES:** Medline, Embase, CINAHL, and PsychINFO databases from January 2000 through June 2014.

**STUDY SELECTION:** Studies reporting long-term neurodevelopmental outcomes based on severity of PIVH were included.

**DATA EXTRACTION:** Study characteristics, inclusion/exclusion criteria, exposures, and outcome assessment data extracted independently by 2 coauthors.

**RESULTS:** The pooled unadjusted odds ratios of the primary outcome of death or moderate-severe neurodevelopmental impairment (NDI) were higher with both mild (1.48, 95% CI 1.26–1.73; 2 studies) and severe PIVH (4.72, 4.21–5.31; 3 studies); no studies reported adjusted odds ratios. Among survivors, odds of moderate-severe NDI were higher with mild and severe PIVH in both unadjusted (1.75, 1.40–2.20; 3 studies; 3.36, 3.06–3.68; 5 studies) and adjusted (1.39, 1.09–1.77; 3 studies; 2.44, 1.73–3.42; 2 studies) pooled analyses. Adjusted odds of cerebral palsy and cognitive delay were higher with severe but not mild PIVH.

**LIMITATIONS:** Only observational studies were included. Fifteen of 21 included studies had a moderate-high risk of bias.

**CONCLUSIONS:** Mild and severe PIVH are associated with progressively higher odds of death or moderate-severe NDI compared with no PIVH, but no studies adjusted for confounders. Among survivors, mild PIVH was associated with higher odds of moderate-severe NDI compared with no PIVH.

Dr Mukerji conceptualized and designed the study, conducted the literature search, performed the initial screening of articles, performed initial analyses, and drafted the manuscript; Dr V Shah screened shortlisted articles to ensure no missing articles for selection, verified the risk of biases for included studies, double-checked all numbers included in meta-analyses and results, and helped revise the manuscript; Dr PS Shah provided statistical supervision, design and methodology supervision, oversaw the analyses, and critically reviewed the manuscript; and all authors approved the final version.

This trial has been registered at PROSPERO (International Database of Prospectively Registered Systematic Reviews; registration number CRD42015017105).

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Periventricular/intraventricular hemorrhage (PIVH) is a frequent complication of prematurity, resulting in brain injury. Its incidence has declined since the 1980s, but because of improvements in neonatal care resulting in increased survival of extremely preterm infants, the absolute number of cases remains high.\textsuperscript{1,2} It occurs in 25\% to 30\% of all very low birth weight preterm infants <1500 g\textsuperscript{3} and the reported incidence in extremely low birth weight infants <1000 g is as high as 45\%.\textsuperscript{4,5}

In preterm infants, PIVH results from bleeding in the germinal matrix, a highly cellular and vascularized layer located between the caudate nucleus and the thalamus at the level of the foramen of Monro, from where neurons and glial cells arise during fetal development.\textsuperscript{6} The germinal matrix starts to involute by 28 weeks and is generally absent in term infants.\textsuperscript{7} Extreme friability of capillaries in the germinal matrix combined with their inability to autoregulate cerebral blood flow makes preterm infants susceptible to PIVH.\textsuperscript{8}

Severity of PIVH is commonly described according to the modified Papile classification\textsuperscript{6,9} as follows: grade 1 PIVH refers to bleeding confined to the germinal matrix; grade 2 denotes PIVH occupying ≤50\% of the lateral ventricle volume; grade 3 PIVH occupies >50\% of lateral ventricle volume, usually leading to distension and dilatation of ventricles; and grade 4 PIVH indicates presence of an infarction and/or hemorrhage in the periventricular white matter ipsilateral to a large PIVH. Even though the classification was based on computed tomography images, cranial ultrasonography (CUS) is most commonly used in the clinical setting to report PIVH. Despite suggestions in recent years to replace this classification system with a more precise and descriptive nomenclature,\textsuperscript{10,11} the Papile criteria remains widely used\textsuperscript{12} in clinical settings, and decisions regarding management and counseling are mostly based on these findings.

Because of the nature of the injury, prognostication of long-term neurodevelopmental outcomes in preterm infants with PIVH has been an active area of research. Low-grade (mild) PIVH, consisting of grades 1 and 2, were previously believed not to increase the risk of neurodevelopmental impairment (NDI) beyond the risk associated with prematurity alone.\textsuperscript{13} However, some recent studies have challenged this notion,\textsuperscript{14,15} whereas others\textsuperscript{16} continue to support the benign nature of mild PIVH. On the other hand, severe grades of PIVH (grade 3 and 4) are well known to be associated with NDI, but there are significant variations in the reported outcomes,\textsuperscript{17–20} which may lead to variability in counseling of long-term outcomes between practitioners. None of the previous reviews have systematically summarized neurodevelopmental outcomes of different grades of PIVH after adjusting for confounders and effect modifiers.\textsuperscript{13} Because of the widespread use of this system, there is a need for a systematic review of this literature with a meta-analysis that will aid neonatologists when providing counseling to parents of preterm infants with PIVH.

**METHODS**

This meta-analysis was conducted and reported as per the guidelines from PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).\textsuperscript{21} The protocol for the review was registered with PROSPERO (registration number CRD42015017105), the international prospective register for systematic reviews (http://www.crd.york.ac.uk/NIHR_PROSPERO).

**Types of Studies**

Observational studies including cohort and case-control studies were included if published in peer-reviewed journals and published after 2000. Studies that followed a cohort of patients enrolled in a previously conducted randomized controlled trial were deemed eligible for inclusion. Only those studies that reported on long-term outcomes based on PIVH severity and did not have a prespecified primary predictor other than PIVH were considered for inclusion. Narrative reviews, letters/editorials, case reports, cross-sectional studies, case series, and dissertations were excluded.

**Types of Participants**

Studies reporting on long-term outcomes in preterm infants (<34 weeks’ completed gestational age [GA]) were included. Studies that included a mix of preterm and late-preterm infants (34–36 weeks’ completed GA) or preterm and term infants (≥37 weeks’ completed GA) were excluded.

**Exposure and Comparison**

To be considered eligible for inclusion, studies must have reported (or provided adequate information to generate) childhood neurodevelopmental outcome data adequate for at least 1 of the following comparison groups:

- Comparison 1: mild PIVH versus no PIVH
- Comparison 2: severe PIVH versus no PIVH
- Comparison 3: severe PIVH versus mild PIVH

Specifically, studies that did not distinguish between mild and severe PIVH were excluded. Furthermore, studies that reported outcome of severe PIVH versus a combination of no PIVH and nonsevere PIVH were excluded. The highest grade of PIVH reported (on either left or right side) for an individual patient was used for classification purposes.

The determination of mild and severe PIVH was based on the aforementioned
modified Papile criteria. As such, only studies that classified PIVH based on the modified Papile criteria (or provided adequate information to do so) were included. Mild PIVH consisted of grade 1 and/or 2 PIVH, whereas severe PIVH consisted of grade 3 and/or grade 4 PIVH. Presence of additional CUS anomalies such as intraparenchymal echodensity/echolucency, porencephalic cysts, and/or periventricular leukomalacia were not a cause for exclusion but were noted.

Outcomes

Studies were included if they provided outcome data for ≥1 of the following aforementioned comparison groups.

Primary Outcome

1. Composite of death or moderate-severe NDI at 18 to 24 months. Moderate-severe NDI was defined as ≥1 of moderate to severe cerebral palsy (CP; as determined by using the Gross Motor Functional Classification Scale for CP or a comparable, validated assessment tool); moderate to severe cognitive delay (assessed per the Bayley Scales of Infant Development [second or third edition] Mental Developmental Index or a comparable validated scale); severe visual impairment, defined as visual acuity <6/60 (metric scale) in the better eye; or severe hearing impairment, defined as requirement of unilateral/bilateral hearing aids or cochlear implants.

Secondary Outcomes

2. Death before 18- to 24-month follow-up.
3. Moderate to severe NDI at 18 to 24 months, as defined above.
4. CP, as defined above.
5. Cognitive impairment, as defined above.
6. Neurodevelopmental outcomes at 3 to 18 years, as assessed by a standardized, validated tool.

Planned sensitivity analyses included studies with and without >30% loss to follow-up and meta-analysis of primary outcome with and without studies with a high risk of bias. Planned subgroup analyses for the primary outcome included analyses of GA ≤28 weeks and >28 weeks, as well as infants <1000 g and 1000 to 1500 g at birth.

Review Methods

Search Strategy

The search strategy was designed in conjunction with an information

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Risk of Bias for Included Studies as per Modified Newcastle-Ottawa Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors, Year</td>
<td>Selection (Total 4)</td>
</tr>
<tr>
<td>Adams-Chapman, 2008</td>
<td>4 2 2 8</td>
</tr>
<tr>
<td>Ambalavanam, 2000</td>
<td>3 2 2 7</td>
</tr>
<tr>
<td>Ancel, 2006</td>
<td>4 0 2 6</td>
</tr>
<tr>
<td>Beaino, 2010</td>
<td>4 2 2 8</td>
</tr>
<tr>
<td>Bolisetty, 2014</td>
<td>4 2 2 8</td>
</tr>
<tr>
<td>Broitman, 2007</td>
<td>4 0 2 6</td>
</tr>
<tr>
<td>Doyle, 2000</td>
<td>3 0 3 6</td>
</tr>
<tr>
<td>Goldstein, 2013</td>
<td>4 1 3 8</td>
</tr>
<tr>
<td>Hoekstra, 2004</td>
<td>3 0 2 5</td>
</tr>
<tr>
<td>Keichl-Kohlendorfer, 2013</td>
<td>4 0 2 6</td>
</tr>
<tr>
<td>Klebermass-Schrehof, 2012</td>
<td>3 0 1 4</td>
</tr>
<tr>
<td>Merhar, 2012</td>
<td>4 1 2 7</td>
</tr>
<tr>
<td>Neubauer, 2008</td>
<td>3 2 2 7</td>
</tr>
<tr>
<td>O’Keefe, 2001</td>
<td>3 0 1 4</td>
</tr>
<tr>
<td>Patra, 2006</td>
<td>4 1 2 7</td>
</tr>
<tr>
<td>Payne, 2014</td>
<td>4 2 2 8</td>
</tr>
<tr>
<td>Schmidhauser, 2006</td>
<td>4 2 3 9</td>
</tr>
<tr>
<td>Sherlock, 2005</td>
<td>3 0 3 6</td>
</tr>
<tr>
<td>Van de Bor, 2004</td>
<td>3 0 3 6</td>
</tr>
<tr>
<td>Vollmer; 2003</td>
<td>3 0 3 6</td>
</tr>
<tr>
<td>Vollmer; 2006</td>
<td>3 0 3 6</td>
</tr>
</tbody>
</table>
specialist at Mount Sinai Hospital, University of Toronto. The following databases were searched (in English): Embase, Medline, CINAHL, and PsychINFO (all from January 1, 2000 through June 9, 2014). The details of search terms used are available in Supplemental Information 1.

Data Extraction
One author (A.M.) conducted the literature search in conjunction with reference librarians at Mount Sinai Hospital, University of Toronto. After amalgamation of results from the 4 databases, titles and abstracts were used to screen studies by A.M. Of the remaining studies, a standardized screening form was used by 2 authors (A.M. and V.S.) to identify eligible studies based on aforementioned criteria. In addition, studies identified from references were similarly screened and assessed for eligibility. Any discrepancies were resolved by involving the third author (P.S.). Data extraction for included studies regarding study design, patient characteristics, inclusion and exclusion criteria, exposures and comparisons, and outcome assessments were performed by A.M. and double checked by V.S.

Assessment of Risk of Bias
The risk of bias for each included study was assessed by using a modified Newcastle-Ottawa Scale and the following domains were evaluated: selection, comparability, and outcome. A priori, a score of 8 or 9 of 9 was deemed low risk; 6 or 7 of 9, moderate risk; and ≤5 of 9, high risk of bias. Of all included studies in the systematic review, only those with low or moderate risk of bias were deemed eligible for inclusion in meta-analyses. Studies with a high risk of bias would be eligible for results but not meta-analysis. In addition, follow-up loss of >30%, regardless of score on modified Newcastle-Ottawa Scale, was considered a high risk of bias. Assessment of risk of bias was performed by 2 authors (A.M., V.S.), independently and any conflicts were resolved with involvement of the third author (P.S.).

Data Synthesis and Statistical Analysis
Studies deemed not comparable due to clinical or methodological heterogeneity as assessed by the authors were not considered eligible for meta-analysis. Unadjusted and adjusted data from studies eligible for meta-analysis were combined using a fixed effects model for all comparisons of interest. Unadjusted and adjusted odds ratios (ORs) were calculated, reflecting the ratio of odds of the outcome of interest between comparison groups. All analyses were performed using

![Unadjusted pooled ORs for the primary outcome of death or moderate-severe NDI for all 3 comparisons.](image-url)
Heterogeneity and Publication Bias Assessment

Variability in the study design, participants, exposures, outcomes assessed, and biases were evaluated qualitatively to determine clinical and methodological heterogeneity and to assess the appropriateness of pooling studies together by 2 authors (A.M. and V.S.) independently, and discrepancies were resolved by involving the third author (P.S.). Furthermore, Forrest plots were assessed for heterogeneity. Statistical heterogeneity was determined for studies grouped together using $I^2$ values (derived from the $\chi^2$ Q statistic). It was determined a priori that if any comparison for any outcome were to have >10 studies eligible for pooled analysis, a funnel plot was to be generated to assess for publication bias.

RESULTS

Description of Studies

The results of the search, the study selection log, and the number of studies are as shown in Fig 1. Of the 3347 studies resulting from the database searches, 85 full-text studies were evaluated for eligibility, and authors were contacted where necessary to provide clarification or missing data. This process resulted in 20 studies deemed eligible for inclusion.14–16,19,27–42 Additionally, 1 study43 was identified and deemed eligible through searching references of included studies, bringing the final total to 21. Baseline characteristics of the 21 included studies are as shown in Supplemental Information 2. References for all excluded studies, including causes for exclusion, are available in Supplemental Information 3.

Risk of Bias Among Included Studies

The risk of bias, as determined by the modified Newcastle-Ottawa Scale for included studies, is as shown in Table 1. Eighteen studies had a low or moderate risk of bias, and 3 studies with a high risk of bias all lost points on the comparability subscale due to the lack of any adjusted analyses. None of the included studies had a loss to follow-up of >30% among the known survivors at time of discharge.

Mild versus no PIVH

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mild PIVH</th>
<th>No PIVH</th>
<th>Weight IV, Fixed, 95% CI</th>
<th>OR IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bollisetty 2014</td>
<td>74</td>
<td>126</td>
<td>1043</td>
<td>51.0%</td>
</tr>
<tr>
<td>Patra 2006</td>
<td>49</td>
<td>72</td>
<td>258</td>
<td>23.2%</td>
</tr>
<tr>
<td>Payne 2014</td>
<td>27</td>
<td>72</td>
<td>1021</td>
<td>25.8%</td>
</tr>
<tr>
<td>Total</td>
<td>710</td>
<td>2322</td>
<td>100.0%</td>
<td>1.75 (1.40–2.20)</td>
</tr>
<tr>
<td>Total events</td>
<td>150</td>
<td>300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 8.27$, df = 2 ($P = 0.02$); $I^2 = 76%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 4.84$ ($P &lt; 0.00001$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Severe versus no PIVH

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Severe PIVH</th>
<th>No PIVH</th>
<th>Weight IV, Fixed, 95% CI</th>
<th>OR IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams-Chapman 2008</td>
<td>616</td>
<td>1950</td>
<td>2060</td>
<td>39.0%</td>
</tr>
<tr>
<td>Ambalavanan 2000</td>
<td>48</td>
<td>37</td>
<td>146</td>
<td>1.5%</td>
</tr>
<tr>
<td>Bollisetty 2014</td>
<td>40</td>
<td>126</td>
<td>1043</td>
<td>4.1%</td>
</tr>
<tr>
<td>Goldstein 2013</td>
<td>858</td>
<td>1406</td>
<td>4104</td>
<td>50.5%</td>
</tr>
<tr>
<td>Payne 2014</td>
<td>40</td>
<td>181</td>
<td>1021</td>
<td>5.0%</td>
</tr>
<tr>
<td>Total</td>
<td>2613</td>
<td>11078</td>
<td>3361</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>1572</td>
<td>3361</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 6.56$, df = 4 ($P &lt; 0.16$); $I^2 = 39%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 2.60$ ($P &lt; 0.00001$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Severe versus mild PIVH

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Severe PIVH</th>
<th>Mild PIVH</th>
<th>Weight IV, Fixed, 95% CI</th>
<th>OR IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bollisetty 2014</td>
<td>40</td>
<td>74</td>
<td>336</td>
<td>54.5%</td>
</tr>
<tr>
<td>Payne 2014</td>
<td>40</td>
<td>27</td>
<td>270</td>
<td>45.5%</td>
</tr>
<tr>
<td>Total</td>
<td>274</td>
<td>606</td>
<td>101</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>80</td>
<td>101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 0.02$, df = 1 ($P = 0.90$); $I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 5.27$ ($P &lt; 0.00001$)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

FIGURE 3

A. Unadjusted pooled ORs for moderate-severe NDI among survivors for all 3 comparisons. B. Adjusted pooled ORs for moderate-severe NDI among survivors for all 3 comparisons.

PEDIATRICS Volume 136, number 6, December 2015 5
Primary Outcome: Death or Moderate to Severe NDI at 18 to 24 Months

There were 3 studies that provided data on the primary outcome for at least 1 of the 3 comparisons. The results from the unadjusted meta-analyses for the 3 comparisons are shown in Fig 2. Mild PIVH (2 studies, 3508 subjects, unadjusted OR 1.48, 95% confidence interval [CI] 1.26–1.73, $I^2 = 79\%$) and severe PIVH (3 studies, 8830 subjects, unadjusted OR 4.72, 95% CI 4.21–5.31, $I^2 = 97\%$) were both associated with higher odds of death or moderate-severe NDI compared with no PIVH. Severe PIVH was associated with a higher odds of death or moderate-severe NDI at 18 to 24 months (2 studies, 1584 subjects, unadjusted OR 3.35, 95% CI 2.69–4.16, $I^2 = 97\%$) compared with mild PIVH. None of the studies provided adjusted analyses for death or moderate NDI. In all 3 studies, mortality rates were provided by PIVH severity, and adjusted outcome analyses were only performed among those known to have survived at least until discharge. Furthermore, all studies included infants ≤28 weeks’ GA and/or a birth weight ≤1000 g, and thus subgroup and sensitivity analyses planned a priori could not be performed. All studies had a low or moderate risk of bias.

Secondary Outcome: Moderate to Severe NDI at 18 to 24 Months

Seven studies reported unadjusted and adjusted ORs for at least 1 of the 3 comparison groups. The results from the unadjusted meta-analyses are shown in Fig 3A, and the adjusted meta-analyses are as depicted in Fig 3B. Mild PIVH was associated with higher odds of the outcome compared with no PIVH (5 studies, 13 691 subjects, unadjusted OR 3.36, 95% CI 3.06–3.68, $I^2 = 39\%$; 2 studies, 2670 subjects, adjusted OR 2.44, 95% CI 1.73–3.42, $I^2 = 82\%$). Finally, severe PIVH was associated with higher odds of moderate-severe NDI when compared with mild PIVH among survivors (2 studies, 880 subjects, unadjusted OR 2.62, 95% CI 1.83–3.74, $I^2 = 0\%$; 2 studies, 1686 subjects, adjusted OR 2.16, 95% CI 1.36–3.43, $I^2 = 0\%$).

Other Secondary Outcomes: Death, CP, and Cognitive Delay

Results from meta-analysis of unadjusted and adjusted ORs (where available) for death, CP, and cognitive delay are reported in Table 2.

Other Secondary Outcomes: Neurodevelopmental Outcome at 3 to 18 Years

Because of the variability in the exposures and reported outcomes

![Figure 3](http://pediatrics.aappublications.org/) Continued.
(both outcome measure as well as timing of outcome assessment), there was deemed to be significant clinical and methodological heterogeneity, and hence, no meta-analyses were performed. Table 3 depicts studies that report various neurodevelopmental outcomes between 3 and 18 years and their primary results. CP was evaluated in 4 of these studies and showed generally incrementally higher rates with worsening grades of PIVH.\(^\text{19,32,34,37}\) Doyle et al reported a lower rate of CP in cases of grade 4 PIVH (20%) compared with grade 3 PIVH (31.2%).\(^\text{32}\) In contrast, Klebermass-Schrehof et al reported rates of CP as high as 90.9% among grade 4 PIVH in their cohort at 5 years of age.\(^\text{34}\) The only study that provided unadjusted ORs for CP at 5 years found no difference in CP with grade 1 PIVH (adjusted OR 1.78, 95% CI 0.94–3.40) but a significantly increased adjusted OR of 29.66 (95% CI 16.71–52.62) when comparing grade 4 with no PIVH.\(^\text{19}\) Although not assessing CP directly, Schmidhauser et al evaluated motor outcomes at 6 years by using the Zurich neuromotor scale and found worsening of pure motor, adaptive fine and gross motor, and static balance with each grade of IVH in a regression model (with only adaptive gross motor decline reaching statistical significance).\(^\text{42}\)

Similarly, studies that evaluated school performance found generally worsening scores despite utilizing a variety of assessment tools.\(^\text{33,38}\) Kiechl-Kohlendorfer et al recently reported that almost 46% and 75% of infants with mild and severe PIVH have delayed numerical skills, respectively.\(^\text{33}\) Van de Bor reported that >20% of children with mild and/or severe PIVH were in special education programs, compared with 8.7% of preterm infants with normal CUS.\(^\text{38}\) Studies reporting composite NDIs at various school ages show similar trends, with infants with both mild and severe PIVH having generally worse impairment than infants with no CUS abnormality.\(^\text{35,39–41}\) One study (O’Keefe et al) reported on visual outcomes alone in patients with CP and found impairment rates of 6.6% and 13.2% with mild and severe PIVH, respectively.\(^\text{36}\) However, none of these studies on school performance or composite neurodevelopmental outcomes reported adjusted outcomes.

**DISCUSSION**

In this systematic review and meta-analysis of long-term outcomes in preterm infants with PIVH, we identified that both mild and severe PIVH were associated with adverse long-term outcomes compared with neonates who did not have PIVH. In particular, mild PIVH was shown to be associated with higher odds of death or moderate-severe NDI, although all studies reporting this primary outcome only provided unadjusted data. There were higher odds of moderate-severe NDI alone in preterm survivors with mild PIVH based on both unadjusted and adjusted data, but no increase in CP or cognitive delay individually at 18 to 24 months. On the other hand, severe PIVH was associated with adverse outcomes in all domains assessed when compared with both no PIVH as well as mild PIVH, with the exception of cognitive delay after adjustment. This suggests that increasing grades of PIVH may have increasing impact on long-term outcomes, and mild PIVH may not be benign as previously suggested.\(^\text{13}\)

However, many of the reported outcomes are based on unadjusted data and must be interpreted with caution.

Our results confirm that severe PIVH leads to worse neurodevelopmental outcomes than mild PIVH or no PIVH and yields specific unadjusted and adjusted ORs that may be valuable during counseling parents of affected infants. Data from the meta-analyses also point to the need for closer surveillance for NDI in those with mild PIVH, and the importance of postnatal interventions and follow-up programs. Although the progressively worse outcomes from none to mild to severe PIVH may suggest a continuum, it must be remembered that the various grades of PIVH represent often distinct pathology.\(^\text{10}\)

The question as to why mild PIVH (limited to the subependymal lining of the germinal matrix [grade 1 PIVH] and/or within the ventricle [grade 2]) without any apparent injury to the brain parenchyma would cause neurologic impairment is important. There are limited human studies evaluating the mechanism of such injury on outcomes, but in vitro

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**TABLE 2 Secondary Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Mild Versus No PIVH</th>
<th>Severe Versus No PIVH</th>
<th>Severe Versus Mild PIVH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UaOR, CI or (n)</td>
<td>aOR, CI or (n)</td>
<td>aOR, CI or (n)</td>
</tr>
<tr>
<td>Death</td>
<td>1.50,(^*) 1.13–2.00</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>No. studies (subject n)</td>
<td>1 (2110)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CP</td>
<td>1.47,(^*) 1.16–1.87</td>
<td>1.00, 0.61–1.64</td>
<td>5.64,(^*) 4.91–6.46</td>
</tr>
<tr>
<td>No. studies (subject n)</td>
<td>4 (4898)</td>
<td>4 (9989)</td>
<td>1 (1202)</td>
</tr>
<tr>
<td>Cognitive delay</td>
<td>1.95,(^*) 1.50–2.53</td>
<td>1.41, 0.97–2.06</td>
<td>1.37, 0.79–2.38</td>
</tr>
<tr>
<td>No. studies (subject n)</td>
<td>4 (3268)</td>
<td>2 (1853)</td>
<td>3 (7922)</td>
</tr>
</tbody>
</table>

\(^*\) OR with statistical significance (95% CI does not cross 1).
<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Patient Population</th>
<th>Outcomes Analyzed and Timing of Follow-up</th>
<th>Main Result(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beaino, 2010</td>
<td>All births between 22 and 32 wk GA in 9 regions of France in 1997 who survived to discharge and completed follow-up at 5 y age (n = 1812)</td>
<td>Outcome: CP. Method/tool: standardized questionnaire with expert review of questionnaires with abnormal neurologic examination. Timing: 5 y.</td>
<td>Adjusted ORs (CI) for CP with no IVH as reference: grade I 1.78 (0.94–3.40); grade II 2.53 (1.30–4.93); grade III 3.25 (2.02–5.22); grade IV 29.66 (16.71–52.62).</td>
</tr>
<tr>
<td>Doyle, 2005</td>
<td>Inborn live births at single site (Royal Women's Hospital, Melbourne) with BW 500–1499 g over 2 eras (18 mo from October 1980, n = 222; 12 mo from January 1992, n = 202)</td>
<td>Outcome: CP. Method/tool: Assessment by developmental pediatrician. Timing: 5 y.</td>
<td>Percentages of survivors with CP within each grade of IVH: none 4.1%; grade I 12.5%; grade II 15.8%; grade III 31.2%; grade IV 20%.</td>
</tr>
<tr>
<td>Hoekstra, 2004</td>
<td>Infants born at GA 23–26 wk between January 1986 and December 2000 who survived (n = 675)</td>
<td>Outcome: normal, mild-moderate impairment or severe impairment in neurologic examination and/or on assessment tools as described below. Method/tool: First 3 y: BSID-II, physical and neurologic examinations; ages 3–6: Denver Developmental Screening Test, Early Language Milestone Scale and Zimmerman Preschool Articulation Test; Children &gt;6 y: University of Vermont Achenbach Child Behavior Checklist, Teacher's Report form. Timing: wide range (mean 47.5 mo).</td>
<td>Percentages of survivors with normal, mild-moderately or severely abnormal assessments, based on IVH. No IVH (n = unknown): 73%, 27%; grade 3 (n = 44): 36%, 64%; grade 4 (n = 39): 21%, 79%.</td>
</tr>
<tr>
<td>Klebermass-Schrehof, 2012</td>
<td>Preterm infants with GA below 32 wk admitted to single NICU in Austria between 1994 and 2005 (n = 471)</td>
<td>Outcome: MDI at 5 y. CP at 5 y visual and acoustic impairment at 5 y. Method/tool: MDI using Bayley Scales of Infant Development at 2 y and KABC at age 5 y. Timing: 5 y.</td>
<td>Percentage of subjects with KABC &lt;70% and CP by IVH: no IVH: 7.6%, 14.3%; grade I IVH: 6.3%, 34.8%; grade II IVH: 12.9%, 55%; grade III IVH: 33.3%, 63.6%; grade IV IVH: 50%, 90.9%.</td>
</tr>
<tr>
<td>Schmidhauser, 2006</td>
<td>Infants with BW &lt;1250 g from single center in Germany born between July 1992 and June 1994 (n = 87)</td>
<td>Outcome: motor performance and movement quality. Method/tool: Zurich neuromotor assessment tool. Timing: 6 y.</td>
<td>β coefficient (SE) and P value in regression model for IVH grades (0–4). Pure motor: –0.08 (0.27); P = .61. Adaptive fine motor: –0.39 (0.27); P = .16. Adaptive gross motor: –0.53 (0.20); P = .009. Static balance: = –0.36 (0.19); P = .07. Associated movements: 0.07 (0.18); P = .67.</td>
</tr>
<tr>
<td>Sherlock, 2005</td>
<td>Infants born &lt;1000 g or very preterm (&lt;28 wk) in Victoria, Australia between January 1991 and December 1992 who survived until age 8 (n = 298)</td>
<td>Outcome: CP, blindness, deafness, intellectual impairments (IQ &lt; –1 SD). Method/tool: Pediatricians and psychologists using Wechsler Intelligence Scale for Children. Timing: 8 y.</td>
<td>Rates of CP, IQ score &lt; –1 SD by grades of IVH. Grade 0: 12/180 (6.7%); 64/180 (35.8%). Grade I: 3/47 (6.4%); 18/47 (38.3%). Grade II: 6/25 (24%); 9/25 (36%). Grade III: 2/12 (16.7%); 7/12 (58.3%). Grade IV: 6/6 (100%); 6/6 (100%).</td>
</tr>
<tr>
<td>Van der Bor, 2004</td>
<td>Infants born in Netherlands at GA &lt;32 wk and/or BW &lt;1500 g at 1 of 8 centers in 1983 (n = 278)</td>
<td>Outcome: Disability or handicaps, school performance. Method/tool: Home visit by 1 of 3 specifically trained pediatricians. Timing: 5 y.</td>
<td>Percentage of children in special education by grades of IVH: no IVH: 17/216 (8.7%); grade I: 3/45 (6.7%); grade II/IV: 2/71 (2.8%).</td>
</tr>
</tbody>
</table>
studies have demonstrated that various blood components have toxic effects in subventricular zone cells and may impair proliferation, differentiation, and migration of oligodendrocyte precursors.44,45 Human neuroimaging studies have also demonstrated quantitative decrease in cortical thickness after uncomplicated subependymal and intraventricular hemorrhage without parenchymal involvement.46 In addition, the contribution of underlying events that lead to mild PIVH and associated fluctuations in systemic and intracranial pressure remains to be elucidated. However, another important consideration is the accuracy of CUS, with a large body of evidence now reporting that CUS may miss parenchymal injury when compared with MRI.47–49 As such, many infants reported to have mild PIVH may have concomitant, but undetected, parenchymal white matter injury that may be contributory to long-term outcomes. This remains an important issue warranting exploration in future studies. However, from a practical standpoint, routine MRI at repeated time points is not feasible, and CUS remains the choice of investigative modality in most NICUs.

The finding of no increase in odds of CP with mild versus no PIVH after adjustment was based only on 1 study16 and may reflect a true lack of or limited effect on the brain parenchyma. More intriguing is the lack of apparent effect on cognitive outcomes at 18 to 24 months after adjustment in both mild and severe PIVH compared with no PIVH. The strengths of the study include the importance and relevance of the question raised and providing quantitative guidance to clinicians when counseling parents of infants with mild or severe PIVH with regard to early childhood outcomes. Other strengths include an extensive English-language literature search; explicit inclusion and exclusion criteria; and a 3-way comparison of mild, severe, and no PIVH. No studies with high risk of bias were included in the meta-analysis of early childhood outcomes adding to the confidence in the reported outcomes. Furthermore, we chose not to meta-analyze school age outcomes due to the clinical heterogeneity of methodology and outcomes.

Among the weaknesses of the review, one relates to the fact that of the 21 included studies, only 5 provided adjusted data for the desired outcomes, and only 2 of these studies...
included postnatal steroids as a covariate. In fact, none of the included studies have reported adjusted outcome measures for death or moderate-severe NDI as a composite outcome, which limits the validity of the primary outcome. The fear with this is that infants with higher grades of PIVH may have had other coexisting pathologies such early-onset sepsis, hemodynamic compromise, or higher ventilation requirements, all of which are associated with PIVH, as well as death and NDI.1,13 Patients with such comorbidities may have had the worst prognosis and may have died while in the NICU or been subject to withdrawal of life-sustaining therapy due to the projected poor outcome. As such, the secondary outcome of moderate-severe NDI in survivors suffers from selection bias because the survivors do not represent the breadth of population first diagnosed with PIVH, and, in turn, the parents of patients who the neonatologist is faced with providing counseling in the acute phase. The same limitation holds true for studies reporting data on mild versus no PIVH, for which none of the studies reported adjusted data for the primary outcome.

Another weakness is the fact that few studies report outcomes by severity of PIVH as well as in comparison with no PIVH. On the basis of the predefined inclusion/exclusion criteria, this unfortunately resulted in the elimination of many large population based studies that reported on long-term outcomes in preterm infant (Supplemental Information 3). Few studies and high variability in reported results from each study led to high statistical heterogeneity. We used a fixed effects model; however, this may call into question our confidence in reported outcomes. There was also a wide birth-year span, ranging from 1992 to 2005 in studies included in the meta-analyses, which covered eras of rapid change in clinical practice; this may have resulted in some clinical heterogeneity between studies. Furthermore, significant clinical and methodological heterogeneity in studies reporting outcomes at 3 to 18 years made a meta-analysis of such studies unfeasible.19,32–42 Finally, some studies report severe PIVH as a combination of grades 3 and/or 4 PIVH along with several other intracerebral lesions such as periventricular leukomalacia, porencephalic cysts, and intraparenchymal echodense lesions, often without separating them from isolated grade 3 and 4 PIVH.19,35,39 This limits our ability to quantify the impact of grade 3 or 4 IVH alone on outcomes of interest. However, in clinical practice, grade 3 and 4 PIVH often coexist with such anomalies.13

CONCLUSIONS
Increasing grades of PIVH may be associated with adverse long-term neurodevelopmental outcomes, and mild PIVH alone may independently have an impact compared with no PIVH. Severe PIVH is associated with a worse outcome compared with both mild PIVH and no PIVH. Neonatologists, follow-up clinicians, parents, and teachers must be cautious in their assessment of infants and children with a history of mild PIVH because these children may need additional resources to maximize their potential. However, further research is required to further elucidate the true effect of mild PIVH on mortality and long-term prognosis of preterm infants.

ABBREVIATIONS
CI: confidence interval
CP: cerebral palsy
CUS: cranial ultrasonography
GA: gestational age
NDI: neurodevelopmental impairment
OR: odds ratio
PIVH: periventricular/intraventricular hemorrhage

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