

Lung and Brain Damage in Preterm Newborns

Are They Related? How? Why?

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Key Words

Infant, premature · Infection · Inflammation ·
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Abstract

The relationships among bronchopulmonary dysplasia (BPD), brain white matter damage (WMD) and cerebral palsy (CP) are far from simple. Apparently, BPD and WMD are not associated, while BPD and CP are. The most likely explanation for this paradox is that ultrasound imaging does not identify all the WMD that might lead to CP ('tip-of-the-iceberg effect'). We discuss further methodological inconsistencies, etiological peculiarities related to antenatal infection/inflammation, and intervention-related issues. In particular, we expand on the multiple-hit scenario in the etiology of BPD and offer support for the hypothesis that it is not lung disease, but factors associated with lung disease (e.g. postnatal steroid exposure) that increase the risk for developmental disability in childhood.

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Introduction

The second-trimester intra-amniotic infection that contributes to preterm delivery directly exposes the fetus to bacterial antigens [1]. Perhaps this exposure to inflammatory stimuli accounts for some of the increased risk of respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), and white matter damage (WMD) seen in infants born much before term. Indeed, clinical observations and experimental data suggest that inflammation plays a role in the pathogenesis of RDS and BPD [2], IVH and WMD [3], and their most prominent developmental adverse sequelae, i.e. cerebral palsy (CP) [4] and cognitive limitations [5].

In this paper, our emphasis is on the relationship between the chronic disorders of the lung and the brain in preterm infants, BPD and WMD/CP. We start with brief descriptions of BPD, WMD and CP. We then outline the paradox arising from the following non-syllogism: (i) ultrasound-defined WMD and CP are associated; (ii) BPD and CP are associated, but (iii) ultrasound-defined WMD and BPD are not associated. We do so in light of the presumed common etiological factor in BPD, WMD, and CP, i.e. antenatal infection/inflammation and discuss

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related pathogenetic issues such as duration of inflammatory exposure and multiple hits in the pathogenesis of WMD [6] and BPD [7, 8].

What's in a Name?

What Is BPD? Traditionally, BPD has been viewed as the major adverse outcome of RDS, ventilation-associated barotrauma, and oxygen toxicity. More recently, a 'new' BPD appears to emerge [9], frequently in very immature babies without typical RDS. This 'new' BPD is conceptualized as a 'developmental disability of the lung', characterized by less, but more diffuse, fibrosis than known from the 'classic' BPD and by an arrest in alveolar development.

Just as the clinical presentation of BPD has varied over the past years, so, too, have its criteria. The more recent definition ('receiving oxygen at 36 weeks' postconceptional age') appears to be a better predictor of abnormal pulmonary signs and symptoms at 2 years than the previously suggested definition of BPD ('receiving oxygen at 28 days of life'), as reflected by positive predictive values of 83 and 38%, respectively [10]. Current consensus favors an even wider definition of BPD as oxygen dependency at 36 weeks' post-menstrual age *plus* a total oxygen exposure for ≥ 28 days [11].

Neonatal ventilation and oxygen exposure, important elements of the definition of BPD, put preterm infants at increased risk for bronchial hyperresponsiveness and asthma [12], suggesting that BPD might be associated with adverse pulmonary sequelae. The question we pose in this article is whether BPD is also associated with WMD and CP.

What Is WMD? White matter damage is the term used for any abnormality identified anywhere in the cerebral white matter, although most often adjacent to the lateral ventricles of preterm infants. No less than 19 different histologic characteristics of WMD have been distinguished [13]. One plausible and comprehensive ultrasound classification system includes three major forms of WMD: unifocal, multifocal, and diffuse [14]. The focal lesions are either hyper- or hypo-echoic, whereas diffuse WMD is characterized sonographically by ventriculomegaly not attributable to post-hemorrhagic hydrocephalus. Disturbances of oligodendrocyte development and/or well-being appear to be an essential part of the pathogenesis of WMD [14].

For epidemiologic purposes, we have recommended the use of the descriptive terms *echodense* and *echolucent*

for any hyperechoic or hypoechoic ultrasound image in cerebral white matter, respectively [15]. Some prefer to subsume under the heading 'WMD' all those clinically well-known ultrasound-defined entities that are consistent with focal *or* diffuse WMD, i.e. cystic periventricular leukomalacia, periventricular hemorrhagic infarction, intraventricular hemorrhage grade IV, persisting echodensities and ventriculomegaly not attributed to post-hemorrhagic hydrocephalus [16]. Neuromotor abnormalities, cognitive abnormalities, and learning disability are the major adverse sequelae of WMD [17].

What Is CP? Cerebral palsy is the best known sequel of WMD and includes multiple clinical disorders of movement and tone [18]. Among preterm infants, bilateral spastic CP is the most frequent subtype, affecting both legs preferentially, although all four limbs and the trunk can also be involved [19]. WMD is considered the most common neuropathological finding of CP in those born preterm and in some born at term [19].

A Paradox?

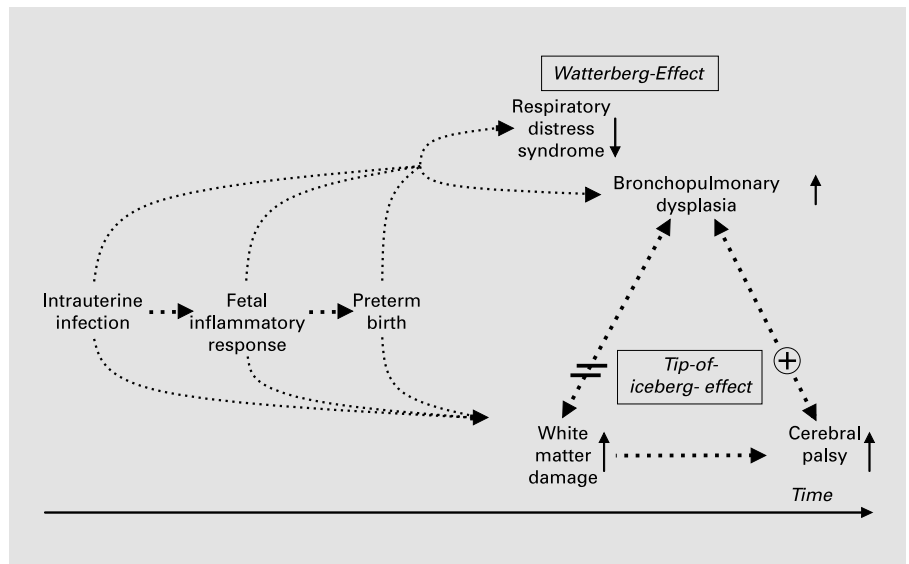
One widely held assumption in neonatology is that phenomena associated with respiratory distress, including BPD, influence the risk of WMD and CP. However, no appreciable association has been observed between BPD and cranial ultrasound abnormalities, such as intracranial hemorrhage [20], subependymal hemorrhage [21], and periventricular leukomalacia [22]. However, a paradox appears to arise from the additional observation that BPD is associated with CP in five studies [23–27], but not in one other study, where CP was more common in controls than in BPD cases [28]. None of these studies employed multi-variable analysis to adjust for potential confounders.

In light of these issues, we recently analyzed a large database of 904 infants born before the 30th week of gestation [29]. In support of the previous findings [20–22], we did not find that BPD (defined as oxygen dependence at 36 postmenstrual weeks) and WMD (defined as echolucency on neonatal ultrasound scans) occur together more frequently than expected by chance. Adjustment for confounders did not help explain this lack of co-occurrence.

Explanations

There are a number of reasons why BPD and sonographically-defined WMD might not be related. These might also help explain why BPD is associated with CP,

Fig. 1. Overview of the scenario that postulates that antenatal infection and inflammation increase the risk of preterm birth, and of damage to the lung and brain in preterm newborns. It also illustrates the inflammation-associated reduced risk for respiratory distress syndrome, but not for bronchopulmonary dysplasia ('Watterberg effect'), and incorporates the finding that bronchopulmonary dysplasia is associated with cerebral palsy, but not with its antecedent, white matter damage ('tip-of-the-iceberg effect').



but not with WMD. In essence, explanations for the apparent paradox outlined above can be discussed at the levels of methodology, etiology, and intervention.

The Most Likely Explanation. The relationship between ultrasound-defined WMD and CP is complex. Consider these facts:

- In multicenter or regional studies, only about half of all preterm newborns who develop CP had ultrasound-defined WMD (for references, see [5]).
- Almost 80% of infants with bilateral echolucencies on a brain ultrasound scan in the neonatal intensive care unit later develop CP [30].
- Approximately two thirds of all infants with unilateral echolucency on a brain ultrasound scan develop CP, most often bilaterally [30].

These and other findings have led to the hypothesis that what is seen on the brain ultrasound scan is only 'the tip of the iceberg' of all the white matter damage that occurs in infants born much before term [14, 30] (fig. 1, bottom box). If support for this hypothesis continues to accrue, then we should expect to see diffuse white matter damage on early magnetic resonance images (MRI) of infants who do not develop an echolucency but later develop CP. Indeed, neonatal MRI might be superior to ultrasound in detecting diffuse WMD [31]. Unfortunately, routine early MRI of the brain of infants born 3–4 months before term is not sufficiently available for epidemiologic research.

Methodological Issues

Chance, Bias, Confounding. Any failure to find that WMD and BPD occur together might be due to chance, bias or confounding, the three classic sources of error in observational research. One way to reduce the likelihood of chance is calculating p values and 95%-confidence intervals for all effect estimates [29]. Nevertheless, a residual likelihood of erroneously rejecting the null hypothesis always remains present, even when smaller than 5%. To minimize bias, cases and controls should be from the same source population of infants, e.g. all should be born before the end of the 30th week of gestation. Moreover, only control infants who survived until 36 weeks' post-menstrual age (the time of BPD diagnosis in our study), and long enough to have a late cranial ultrasound scan to ascertain WMD, should be included. Finally, to reduce the likelihood of confounding, adjustment is needed for multiple factors that are associated with both WMD and BPD [29].

Definitions. Another important methodological source of error might be the definitions used. We define WMD as a single echolucency [29], whereas some others are less than explicit about their criteria or else require bilateral echolucencies for their definition of 'periventricular leukomalacia'. Although definitions differ widely, all studies have failed to find an association between BPD and WMD [20–22, 29].

The definitions of BPD also differ considerably [32]. As indicated above, the currently most frequently used

Table 1. Maternal and fetal inflammatory challenges and early/late abnormalities of the preterm lung/brain

Risk factor	Time of assessment	Lung	Brain
Maternal (POOL/PROM, CAM)	early neonatal	PROM ↓ RDS [72] CAM ↓ RDS [34, 41] CAM ↑ RDS [39] CAM ≈ RDS [69]	CAM ↑ IVH [42, 73–75]
	late neonatal	CAM ↑ BPD [34, 39, 41, 42] CAM ≈ BPD [7] CAM ↓ BPD [40]	PROM/CAM ↑ PVL [76] CAM ↑ cPVL (multiple, summarized in [4])
	infancy/childhood	no data	POOL/PROM ↑ CP [77] CAM ↑ CP (multiple, summarized in [4]) CAM ≈ CP [78, 79] fever ↓ IQ [80]
Fetal (funisitis, cytokinemia)	early neonatal	IL-6/GCSF ↑ RDS [81]	cytokines ↑ IVH [75, 82, 83]
	late neonatal	IL-6 ↑ BPD [43] funisitis ↑ BPD [44] fetal vasculitis ≈ BPD [7]	fetal vasculitis ↑ EL [50, 84]
	infancy/childhood	no data	funisitis ↑ neuro/CP [48, 85, 86] funisitis ≈ CP [78, 79] cytokines ≈ CP [87]

↓ = ‘Is associated with decreased risk for’; ↑ = ‘is associated with increased risk for’; ≈ = ‘is not associated with a risk change for’; BPD = bronchopulmonary dysplasia; CAM = chorioamnionitis; CP = cerebral palsy; EL = echolucency; GCSF = granulocyte colony-stimulating factor; IL = interleukin; IVH = intraventricular hemorrhage; POOL = preterm onset of labor; PROM = prelabor rupture of membranes; RDS = respiratory distress syndrome.

definition is oxygen dependence at 36 weeks’ post-menstrual age.

Etiologic Issues: Inflammation

Intrauterine infection (IUI) is ‘often chronic, and it is usually asymptomatic until labor begins or the membranes rupture’ [1]. This makes IUI a notoriously difficult diagnosis.

In IUI, histologically evident inflammatory responses are frequently observed in placental membranes (chorioamnionitis, CAM) as well as in umbilical cord (funisitis), and chorionic plate (fetal vasculitis, a term used for the presence of either umbilical or chorionic vasculitis) [33]. The association between maternal and fetal inflammatory responses and damage to the neonatal lung and brain is far from simple (table 1).

Infection/Inflammation and BPD. From a rather small study stems what we call the ‘Watterberg effect’ (fig. 1, top box), i.e. the observation that histologic CAM is not only associated with a reduced risk of RDS, but also with an

increased risk of BPD [34]. Indeed, experimental work suggests that exposure to intrauterine infection is associated not only with lung maturation and improved postnatal lung function [35] but also with delayed alveolarization [36].

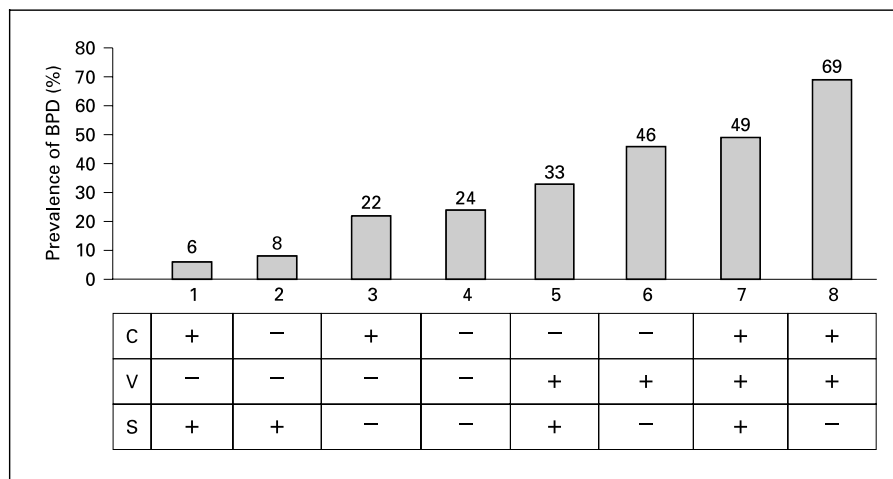
However, available epidemiologic data do not unanimously support this ‘early-protection, late-damage’ scenario purportedly initiated by phenomena that lead to histologic CAM, i.e. a maternal inflammatory response.

First, post-mortem data from human fetuses suggest that histologic CAM is associated with a prominent inflammatory response in the fetal lung [37], similar to the pattern observed in infants who die with RDS [38]. This is in keeping with an *increased* risk for RDS in severe CAM [39], but in discordance with the early-protection concept.

Second, some [7, 40] have not been able to confirm the late-damage concept suggested by others [34, 39, 41, 42].

Third, the data on *fetal* inflammation and BPD are sparse. However, among the few available reports only some [43, 44], but not all [7] support a positive relation-

Fig. 2. Prevalence of bronchopulmonary dysplasia in subgroups defined by the presence (+) or absence (-) of histologic chorioamnionitis (C), mechanical ventilation >7 days (V), and postnatal sepsis (S). These data from Van Marter et al. [88] support the hypothesis that ‘multiple hits’ tend to increase the risk of BPD more than single hits.



ship between fetal vasculitis and BPD. In one additional study [45], funisitis with arterial inflammation was associated with BPD, while funisitis without arteritis was not. Thus, data from human newborn populations appear to support the experimental data only partially.

Infection/Inflammation and WMD/CP. In the early 1970s, perinatal neuroepidemiologists found that neonatal receipt of antibiotic, an indicator for infection or a risk factor in its own right, and bacteremia diagnosed at post mortem examination were significantly associated with histologic evidence of WMD [46]. To this day, no one has reported that bacteria actually need to gain access to the fetal brain to cause WMD. Thus, the concept of remote infection in WMD/CP etiology [47] still awaits refutation.

CAM is now widely accepted as a risk factor for neonatal brain WMD and later neurodevelopmental disability. However, pooled studies suggest that the risk of CP is doubled in infants whose mother had clinical or histological CAM [4], while the relative risk for CP and other neurodevelopmental dysfunctions is considerably higher among preterm infants whose placenta showed evidence of chorionic plate inflammation [48, 49]. The risk of echolucency is highest among preterm infants who had vasculitis of the chorionic plate and/or umbilical cord [50]. The prominent risk increase for WMD [51–53] in preterm infants with elevated systemic cytokine concentrations provides additional support for the view that the fetal inflammatory response might be more harmful for the fetal brain than maternal inflammation [54].

Multiple Hits. Both antenatal exposure to glucocorticoids and inflammation appear to increase fetal pulmo-

nary susceptibility to subsequent adverse exposures (‘hits’) [8]. Indeed, both experimental [55] and observational data [7] support the hypothesis that multiple hits might lead to a much more prominent risk increase than just one. We expand on the ‘multi-hit hypothesis’ by offering the following suggestions, based on data from Van Marter et al. [7] (fig. 2).

First, antenatal inflammation *alone* might not affect [7] or even reduce the risk for BPD [40]. On the other hand, antenatal inflammation might prime the lung to be more susceptible to subsequent hits. In the two twin-column constellations that include mechanical ventilation >7 days (fig. 2), adding CAM (i.e. going from columns 5 to 7 and 6 to 8) is associated with a slight risk increase for BPD. However, in the two otherwise similar constellations that do not include mechanical ventilation >7 days (columns 1/2 and 3/4), adding CAM (i.e. going from columns 2 to 1 and 4 to 3) is not associated with an appreciable risk change. This can be interpreted as support for the hypothesis that CAM alone does not affect BPD risk in the absence of subsequent prolonged mechanical ventilation.

Second, in all constellations, adding mechanical ventilation >7 days (going from 2 to 5, 4 to 6, 1 to 7, and 3 to 8) is associated with a prominent BPD risk *increase*. This might be due simply to the fact that prolonged ventilation is almost part of the BPD definition we used. Moreover, long ventilation might be an innocent bystander variable of severe illness or, even worse, be a consequence of BPD.

Third, in all constellations, adding postnatal sepsis (going from 3 to 1, 4 to 2, 6 to 5, and 8 to 7) is associated with

a prominently *decreased* risk for BPD. The risk was lowest (6%) among infants who had CAM and postnatal sepsis, but were not ventilated for more than 1 week.

On the other hand, multiple studies have confirmed that CAM [4], prolonged ventilation [29], and neonatal sepsis [56–58] are risk factors for WMD. Thus, one explanation for the absence of an association between BPD and WMD might be differential organ-specific effects of multiple inflammatory hits, which might be at least partially beneficial for the neonatal lung (in the absence of prolonged ventilation), while being harmful for the developing brain.

All of the previous interpretations of the data in figure 2 have to be viewed with caution. Large-scale studies, uniform definitions of diagnoses, and multivariable data analyses within each group (represented by a single column in fig. 2) are needed to confirm the associations discussed above.

We still do not know if multiple hits play a role in the pathogenesis of WMD in human infants. The multifactorial model, however, seems to apply to every human disease studied so far. However, even if multiple hit scenarios apply to both BPD and WMD, it is unlikely that the same hits in the same infant necessarily lead to both BPD and WMD. Bacterial products, such as lipopolysaccharide (endotoxin), not only can alone produce WMD (for an overview, see [59]), but can also increase damage following a second exposure [6] (sensitization), and reduce damage following other insults (preconditioning/tolerance) [60]. In contrast to the CAM-BPD relationship, no one to our knowledge has ever shown that antenatal infection/inflammation protects the fetal brain.

Duration of Antenatal Exposure to Inflammation. We do not assume that the only possible pathogenetic mechanism for lung and brain damage is damage to existing structure by a time-limited insult. Long-standing exposure to an unfavorable milieu, followed or accompanied by an alteration of normal developmental processes, also appears to be a plausible model. Moreover, interactions between the two scenarios, as in preconditioning (see above) [6], should be considered.

Alteration of developmental processes takes time. Currently, only very limited information is available regarding the duration of exposure to infection/inflammation and risk for BPD and WMD.

Some pathologists distinguish between acute and subacute (or chronic) CAM [41]. In acute CAM, ‘well-preserved polymorphonuclear leukocytes (are) distributed continuously from the intervillous space to the amnion’, while subacute CAM can be defined as present when ‘the

inflammation (is) maximum in the amnion, less severe in the chorion and minimal in the intervillous space’ [41]. Using these definitions, subacute, but not acute, CAM is associated with an increased risk for BPD [41]. One interpretation of this finding is that long-standing exposure to antenatal inflammation might be associated with a risk increase for BPD, while exposure of short duration is not.

Only 50% of preterm newborns exposed to phenomena that lead to histologic CAM also have fetal vasculitis, whereas almost all preterm newborns who have fetal vasculitis also have CAM [50]. These observations support the view that fetal vasculitis is a marker of the severity/duration of CAM. Thus, it should not be surprising that the increased risk of WMD associated with CAM is most evident in infants who also had fetal vasculitis [50]. This increased risk is seen most prominently in pregnancies in which delivery occurred within 1 h of membrane rupture, supporting the view that the severe inflammation began sufficiently before delivery to damage the brain. Fetal vasculitis that accompanies prolonged rupture of the membranes, and therefore presumably of more recent onset, is not associated with appreciably increased risk of WMD [61].

Intervention Issues: Glucocorticoids

Antenatal Glucocorticoids. Both antenatal inflammation and glucocorticoid exposure appear to improve postnatal lung function [35]. Both also increase average alveolar volume, but decrease the number of alveoli [36]. These prominent similarities between the pulmonary effects of antenatal inflammation and glucocorticoids suggest that they might be biologically related.

However, experimental studies have shown that the effects of inflammation on lung development can occur without elevated glucocorticoid levels [62], although clinical observations suggest an increase in endogenous glucocorticoid production in inflammation-exposed fetuses [63, 64]. Also, surfactant production appears to be stimulated by inflammatory challenge more than by glucocorticoid, while concurrent exposure to both stimuli does not result in a further increase [65].

In two large observational studies, antenatal glucocorticoid therapy was *not* associated with a decreased risk of BPD [66, 67]. Conversely, antenatal glucocorticoid and inflammatory exposure appear to have opposite effects on the developing brain. In essence, inflammation is harmful (see above) while glucocorticoids are protective [68], apparently even in the presence of histologic membrane inflammation [69]. Since antenatal glucocorticoids are now frequently used in pregnancies at highest risk, those

who would formerly have developed both BPD and WMD might nowadays be spared from WMD, while still developing BPD.

Postnatal Glucocorticoids. If postnatal glucocorticoid treatment is effective in BPD prevention [70] but also increases the risk for neurodevelopmental disability [68, 71], exposure to postnatal glucocorticoids might help explain why BPD and WMD are not associated in some studies [20–22, 29]. The finding that BPD appears to be associated with cerebral palsy [23–27] could be explained, if infants with established BPD were treated with postnatal glucocorticoids.

Conclusions

We suggest that future research be designed to identify the respective roles of infection and inflammation when studying risk patterns in newborns. We further suggest separating maternal (CAM) and fetal inflammation (fetal vasculitis), at least until data are available in support of the claim that both play identical roles in the pathogenesis of neonatal disorders.

Future epidemiologic studies need to be large, use well-defined diagnoses, and employ time-oriented risk models, adjusting models that focus on late risk factors (BPD) for confounders that occur earlier (e.g. inflammation and glucocorticoid exposure).

Future basic research will need to identify aspects common to developmental abnormalities in surfactant and myelin production, both being lipid-protein mixtures

with important roles in lung and brain development, respectively.

We await studies that address the question whether infants who develop BPD are more likely than their peers to have diffuse WMD on MRI. Follow-up of infants in this type of study would then be able to evaluate to what extent the increased risk of CP in infants with BPD is due to diffuse WMD not detectable by ultrasound.

In sum, the relationships among BPD, WMD and CP are far from simple. Apparently, BPD and WMD are not associated, while BPD and CP are. The most likely explanation for this paradox is that ultrasound imaging does not identify all the WMD that might lead to CP. MRI scanning of the brain among preterm infants most at risk of CP will help clarify this issue. This apparent paradox might also be explained (if not resolved) by methodological inconsistencies, etiological peculiarities, and intervention-related issues. However, the absence of an association between BPD and the *earlier* variable for perinatal brain damage (WMD) offers at least some support for the hypothesis that it is not lung disease that increases the risk for developmental disability in childhood, and that factors associated with lung disease (e.g. postnatal steroid treatment) might be the culprit.

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