Defining Very Preterm Populations for Systematic Reviews With Meta-analyses

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A tale of missing studies: defining very preterm populations for systematic reviews with meta-analysis

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Introduction

Survival of very preterm (VPT) infants (< 32 weeks' gestation) has improved markedly over recent decades, raising concerns about levels of impairment among survivors. Numerous studies have been conducted on the association between VPT birth and long-term neurodevelopment and health, and this voluminous literature is increasingly synthesized in systematic reviews with meta-analyses. This methodology is considered to provide the highest level of evidence, but its validity depends on appropriate selection of primary studies and management of heterogeneity. Heterogeneity is pervasive in the VPT literature because of differences in criteria for defining preterm populations, study designs, follow-up periods, follow-up rates and clinical assessments. Further, medical practices, survival and morbidities vary markedly across countries and hospitals and can impact on long-term prognosis. We aimed to compare the selection criteria, findings and heterogeneity of systematic reviews with meta-analyses of VPT cognitive outcomes, which are of major concern in this population and measured in most studies.

Methods

We searched for systematic reviews with meta-analyses based on observational studies with cohort designs investigating general cognition (IQ) for VPT children in comparison with term controls (search terms available from authors). Two researchers (MS, JZ) independently abstracted methods and results related to study selection, pooled analyses and heterogeneity. We compiled primary studies and identified unique cohorts when several studies originated from the same cohort based on the country, birth year(s), and research group.

Results

Five reviews were identified: 1 in 2012[1] and 4 published in 2018/2019[2-5]. All investigated the impact of birth <32 weeks on childhood IQ, although some also considered other outcomes or sub-groups. Eligibility criteria varied for birthweight, assessment ages and period (Table).

Authors searched Medline,[1-5] Embase,[1,2] PsychInfo[1,3-5] and WoS,[3,4] using different search terms.

A total of 156 primary studies reporting results from 114 VPT cohorts were included in all reviews. Among 111 cohorts in the three 2018/2019 reviews without upper limits on assessment ages, only 8 were in all three (Figure). When these were limited to the 58 cohorts covered by studies published before 2009 to permit comparison with the 2012 review, none was in all four reviews and 35 (60%) were in one review only. All 7 cohorts in the review on assessments at three to five years[5] were in at least one other review, but none was in all three.

All reviews reported lower IQ among VPT compared to term children (pooled effects from -0.77 to -0.86 standardized mean difference or 11.6 to 12.9 IQ points for results relating to all children born <32 weeks). Most showed moderate to high heterogeneity overall or in at least one GA sub-group (I^2>60%).

Discussion

Investigators' methodological choices had a strong impact on primary study selection in systematic reviews with meta-analyses on VPT birth and cognition despite shared objectives. - representing a missed opportunity to synthesize all available information and raising questions about appropriate criteria for selecting studies in this population. Nonetheless, similar pooled estimates affirmed the robust conclusion that VPT birth lowers IQ, although with substantial inter-study heterogeneity.

The exponential increase in systematic reviews with meta-analyses has called attention to the need to organize research efforts in order to avoid both redundant and contradictory results when evidence is synthesized.[6] Continued investigation of the long-term consequences of VPT is essential to address concerns about high and stable impairment rates in VPT survivors and to investigate variation related to perinatal management, follow-up services and the socio-cultural

environment. Establishing common guidelines to select primary studies, along with open-access repositories of studies from previous reviews, would ensure that future reviews use all relevant information and optimize the analysis of inter-study heterogeneity.

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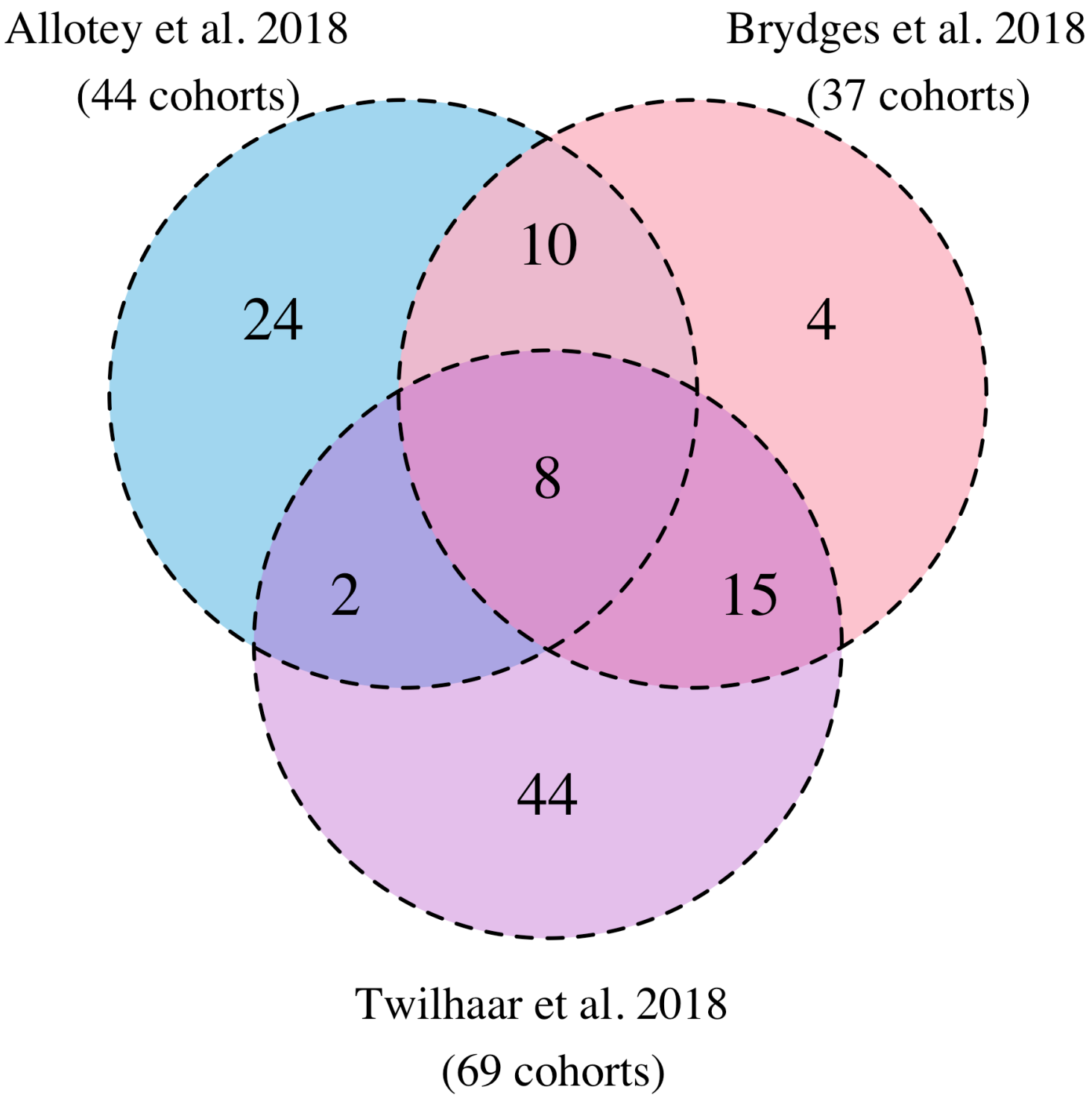
Table 1 – Inclusion criteria, search terms and principal results in systematic reviews with meta-analyses of cognitive outcome after very preterm birth

	Kerr-Wilson 2012[1]	**Allotey 2018[2]**	**Brydges 2018[3]**	**Twilhaar 2018[4]**	**Arpi 2019[5]**
Gestational age (GA) and/or birthweight (BW) criteria	GA<37 weeks (groups <28/28-31 weeks), BW not mentioned	GA< 37 weeks (groups <28/28-33 weeks), BW not mentioned	GA <32 weeks, exclusion of studies based on BW only	GA< 32 weeks and/or BW<1000g or <1500g	GA< 32 weeks and/or BW <1500g
Assessment age	≥4 years	≥2 years	Mean age 4 to 17 years	≥5 years	3 to 5 years
Time period	Published 1980-2009	Published 1980-2016	Published <07/2017	Published <03/2017; birth ≥1990 (1)	Published 2000-2017; birth>1994
Other criteria	No	Yes (2)	Yes (3)	No	No
Search terms for preterm population	Preterm, low BW, GA, date of delivery, prematur*, baby/ies, or infan*	(Preterm, pre-term, pre term, premature, near-term, prematurity AND birth, infant, delivery, baby/ies) OR exp prematurity (4)	Low BW, premature*, preterm AND child*	Prematur*, preterm, low birthweight, elbw, vlbw	Preterm birth, premature, low BW AND preschool* or preschool age
N of studies/cohorts on VPT (5)	21/21	50/44	44/37	71/69	7/7
Pooled estimate for VPT (SMD and 95%CI) (6)	<28 weeks -0.95 (-1.09;-0.80); 28-31week: -0.84 (-0.97;-0.71) (7)	<28 weeks: -0.78 (-0.85;-0.72); 28-33 weeks: -0.73 (-0.78;-0.67)	<32 weeks -0.82 (-0.90; -0.74)	<32 weeks: -0.86 (-0.94; -0.78)	<32 weeks: -0.77 (-0.88; -0.66)
Heterogeneity (I^2)	66.5% (<28 weeks) 48.4% (28-31 weeks)	35.3% (<28 weeks) 63.7% (28-33 weeks)	62.9%	74.1%	0%

Notes (1) Or cohort born <1990 if with antenatal steroid or surfactant therapy (2) Excluded if correction for chronological age at assessment (3) Excluded if restrictions were placed on participants based on task performance (4) "exp" indicates that the subject heading "prematurity" was "exploded" to include narrower subject headings included in its tree structure. (5) VPT defined as GA<32 weeks[1,3-5] or GA<34 weeks (3 of the 44 cohorts at 32/33 weeks)[2] ; (6) SMD=Standardized mean difference in IQ scores (VPT children – FT children) and 95% confidence interval; (7) SMD was computed from the weighted mean difference reported by the authors (<28 weeks: 13.9 (11.5; 16.2); 28-31 weeks: 11.4 (9.7; 13.2))

Figure 1 – Overlap of 111 cohorts included in three 2018 systematic reviews with meta-analyses of the impact of very preterm birth on cognition


Allotey et al. 2018
(44 cohorts)
Brydges et al. 2018
(37 cohorts)
24
10
4
8
2
15
44
Twilhaar et al. 2018
(69 cohorts)