Population-based studies of brain imaging patterns in cerebral palsy

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AIM The aim of this study was to review the distribution of neuroimaging findings from a contemporary population cohort of individuals with cerebral palsy (CP) and to facilitate standardization of imaging classification.
METHOD Publications from 1995 to 2012 reporting imaging findings in population cohorts were selected through a literature search, and review of the titles, abstracts, and content of studies. Relevant data were extracted, including unpublished data from Victoria, Australia. The proportions for each imaging pattern were tabulated, and heterogeneity was assessed for all individuals with CP, and for subgroups based on gestational age, CP subtype, and Gross Motor Function Classification System level.
RESULTS Studies from three geographic regions met the inclusion criteria for individuals with CP, and two additional studies reported on specific CP subtypes. Brain abnormalities were observed in 86% of scans, but were observed least often in children with ataxia (24–57%). White matter injury was the most common imaging pattern (19–45%), although the proportions showed high heterogeneity. Additional patterns were grey matter injury (21%), focal vascular insults (10%), malformations (11%), and miscellaneous findings (4–22%).
INTERPRETATION This review suggests areas where further dialogue will facilitate progress towards standardization of neuroimaging classification. Standardization will enable future collaborations aimed at exploring the relationships among magnetic resonance imaging patterns, risk factors, and clinical outcomes, and, ultimately, lead to better understanding of causal pathways and opportunities for prevention.

Cerebral palsy (CP) is a clinically diagnosed syndrome with multiple aetiological pathways.[1] Adverse events occurring at different developmental stages can result in the same clinical pattern of CP, whereas a similar pathway may produce variable outcomes.[2] By providing an in vivo view of brain structure, brain imaging can help to clarify the nature and timing of the insult to the brain.[2–5] Early imaging is often performed in children with neonatal complications, to provide an accurate determination of the pathogenic mechanism and to inform decisions about early treatment, prognosis, and ongoing medical management.[3] In many children, however, the neonatal period is unremarkable, and motor problems are not appreciated until later in infancy or childhood. At the investigation stage, determination of the nature and timing of the brain abnormality through imaging and clinical history is important for assessment of the recurrence risk, counselling of families, medico-legal purposes, and to limit unnecessary testing.[3] Better categorization of imaging patterns is likely to play a

pivotal role in deepening our understanding of the aetiological pathways of CP: a crucial step in the ongoing search for preventative strategies.

Three reviews have reported imaging findings in CP. Ashwal et al.,[3] on behalf of the American Academy of Neurology, amalgamated magnetic resonance imaging (MRI) data pertaining to 644 children across 10 studies. Abnormalities were identified in 89% of scans, although the proportion of abnormal scans depended on the type of CP, whether the child was born preterm or at term, and whether or not the insult was acquired postneonatally. The 2004 review included practice parameters recommending that neuroimaging be routinely performed in children with CP if the aetiology had not already been established, for example by neonatal imaging, and that MRI should take precedence over computed tomography (CT), because of its better detection rates.[3] As the American Academy of Neurology recommendations were based on evidence from only one population-based study and two convincing

non-referral clinic-based samples,[3] questions were subsequently raised about whether the literature available at that time provided adequate evidence to support the development of practice parameters on the timing of the cerebral injury[6]; there was also criticism of the development of recommendations based on evidence from studies not representative of all CP.[7] In 2007, Krägeloh-Mann and Horber[8] reviewed MRI studies published between 1990 and 2006. Of the six studies meeting their inclusion criteria, only one was population based and there was over-representation of children born preterm. Abnormal MRI findings were present in 86% of children with spastic or dyskinetic CP. In 2008, Korzeniewski et al.[2] extended the earlier work of the American Academy of Neurology by examining the degree to which neuroimaging contributes to our understanding of the causes of CP. Only two of the identified studies published between 1970 and 2006 were population based and included all CP subtypes.[4,9] Among 20 studies that included multiple forms of CP, 80% of scans exhibited imaging abnormalities, 86% with MRI and 74% with CT. The studies differed on whether all findings were reported or whether just the principal finding was reported. Before grouping CP into five categories, more than 100 separate terminologies were used to describe the abnormalities, highlighting the need for consistent, standardized reporting and classification of brain abnormalities in CP.

Since these reviews were performed, progress has been made towards a standardized system for classifying imaging findings. Initial classifications were based on a combination of anatomical, pathological, and aetiological descriptors of either all findings or the principal finding, and, for comparison purposes, these needed to be reclassified by the reviewers into one or more broader categories. More recently, published imaging findings from population cohorts have already been classified into fewer, mutually exclusive, and comparable patterns. These patterns are based on contemporary knowledge about the genetic and environmental susceptibilities of specific regions and cells to insults during various periods of brain development,[10] and therefore provide some insight into the possible pathogenesis. Broadly following the classification developed by Krägeloh-Mann and Horber[8] in their 2007 review, most reviews include categories for normal scans, brain malformations, and white matter injury (WMI); this reflects the pattern frequently seen in children born before 34 weeks' gestation.[11] Additional categories are focal vascular insults, the most common of which is infarction in the territory of the middle cerebral artery, and a group of patterns in which the insult primarily affects the cerebral cortex/subcortex and/or deep grey matter bilaterally. Grey matter injury (GMI) has been described following acute hypoxic–ischaemic, inflammatory, or metabolic insults in infants born near term.[12]

Even with comparable classification systems, variation in the distribution of findings between geographic cohorts may be accentuated if similar methodologies are not used. First, classification may be affected by whether or not account was taken of the past history or clinical details.

What this paper adds
- Of children with CP, 86% had abnormalities detected on brain imaging.
- Normal neuroimaging was particularly associated with ataxic CP.
- Malformations and focal vascular insults were consistently reported between population studies but white matter injury showed high heterogeneity.
- This review suggests ways to improve consistency in the classification of neuroimaging in CP.
- The first review to present imaging findings in CP by GMFCS level.

Blinding reduces the opportunity for assessors to be influenced by known associations between MRI patterns and clinical information, but may also make interpretation of some MRI findings more difficult. Second, two related issues revolve around which scans should be classified in the case of serial scans, and whether a lower limit should be set for the age at which imaging is performed. This is particularly relevant for WMI, since before the age of 3 years distinguishing a white matter abnormality from normal unmyelinated white matter in the peritrigonal regions can be difficult.[13] Third, the training and expertise of the person assessing the scans has been shown to affect reliability; one study found that 60% of brain MRI scans reported as normal by general radiologists were found to be abnormal on specialist review.[14] Finally, consensus is required regarding the treatment of dual or multiple patterns of injury.

In light of the emergence of comparable classification systems originating from population-based CP registries, potential increases in the number of children with CP who have imaging, and improvements in MRI technology and interpretational expertise, our primary aim was to review the distribution of imaging findings from contemporary population cohorts. To build on the knowledge gained from previous reviews, we aimed to present the distribution of imaging patterns for all children with CP not only by subtype and by time of birth, but also by Gross Motor Function Classification System (GMFCS) level. In the interests of moving towards universal adoption of a standardized and reliable classification of imaging in CP, our second aim was to assess current progress towards standardization by comparing the definitions and distributions between geographic cohorts, and to suggest areas in which further discussion might be needed to achieve this. Reaching consensus about a reliable classification system is a research priority and will facilitate investigation of causal pathways in more pathogenically homogeneous groups. This may prove the key to improving our understanding of causation in CP, and open the door to the development of new preventative strategies.

METHOD

This review was conducted at the Murdoch Childrens Research Institute in Melbourne, Australia, with ethics approval from the Melbourne Royal Children's Hospital Human Research Ethics Committee. No review protocol was registered before commencement of the study.

Selection of studies and eligibility criteria

The first author conducted a literature search using MEDLINE for articles published in English between 1995 and

2012. The search terms used were 'cerebral palsy/epidemiology' OR 'cerebral palsy/diagnosis' (MeSH), AND 'neuroimaging' OR MRI (keywords). Titles and abstracts were independently reviewed for content by the first author. Data were included from articles originating from industrialised nations in which a population sample was used. We included studies based on findings from MRI and CT when CT accounted for less than half of the total number of scans assessed. For all CP cases, data were excluded if fewer than 100 scans were assessed and if less than half the population sample were imaged. When possible, children with CP associated with a postneonatal injury were excluded.

In addition to the cohorts found as part of the review process, we included data from a large, unpublished cohort identified from the Victorian Cerebral Palsy Register. These data were obtained as a result of the classification of 594 available MRI scans of children with non-postneonatally acquired CP who were born in the Australian state of Victoria between 1999 and 2006. The methodology was informed by an earlier study performed using a subgroup of these children born in 2000 and 2001.[15] For the current review, however, the classification system was modified and the scans were reassessed.

Data collection and analysis
For each article meeting the study inclusion criteria, the first author extracted data on the methods used, the year of publication, the sampling frame, the proportion of the population included, the total number of assessed scans, the CP subgroups included, the imaging classification and definitions used, and the number of children with each imaging pattern. For consistency, five cases of intracranial haemorrhage and three cases of infection in one study were reclassified as miscellaneous, and different categories of GMI were combined.[16] Data on the distribution of imaging patterns were also assembled for subgroups based on CP subtype (spastic motor types of hemiplegia, diplegia, quadriplegia, bilateral spastic CP and all spastic CP, as well as dyskinetic and ataxic motor types), term or preterm birth, and GMFCS level.[17] Potential sampling bias in individual studies was noted if data comparing the characteristics of those with and without imaging were presented. Whether assessors were blind to clinical details was recorded to assess the potential for classification bias.

For each study, the proportions of each imaging pattern were tabulated, with their 95% confidence intervals, for all CP cases and for subgroups based on term or preterm birth, CP subtype, and GMFCS level. The heterogeneity of the estimates for each imaging pattern was assessed using the I^2 statistic, which measures the percentage of total variation across registries due to heterogeneity.[18] Values for I^2 lie between 0% and 100%, with a value of 0% indicating no observed heterogeneity, and larger values indicating increasing heterogeneity. After examining the data, we assigned categories of low, moderate, and high heterogeneity to I^2 values of 25%, 50%, and 75%

respectively. Data were synthesized using weighted means only if heterogeneity was low. Analysis was performed using STATA 12.0 software (Stata Corp. 2011, College Station, TX, USA).

RESULTS
Studies from five regions, (Western Sweden, South-west Germany, Quebec, California, and unpublished data from Victoria, Australia), met the review inclusion criteria for all CP cases, or for the chosen subgroups (Table I, Fig. 1).[9,16,19,20,22,23] Data from two successive Swedish cohorts were combined.[9,19] The definitions and/or inclusions used for each imaging pattern are summarized in Table II.

Distribution of MRI/CT patterns for all CP cases
The distribution of MRI/CT patterns, representative of all individuals with CP, was obtained from studies undertaken in Quebec,[16] Sweden,[9,19] and Victoria. Studies from California and Germany could not be included because data were presented only for selected CP subgroups. In the Quebec study,[16] it was unclear whether postneonatally acquired CP was included.

In the Quebec study, imaging data were extracted from the Quebec CP registry.[16] Classification of 126 MRI and 87 CT scans was performed from paediatric neuroradiology reports by a neurologist, blinded to clinical variables. In the case of multiple scans, the latest one was given preference. There was no lower age limit for inclusion. Although a minority of images showed more than one abnormality, it was not stated how these were classified. Comparatively fewer children born before 37 weeks' gestation, from a twin pregnancy, or with spastic diplegia had imaging performed, whereas children with severe neonatal encephalopathy and those with severe impairment were more likely to have imaging available.

Data from Sweden came from a long-running CP registry covering a well-defined area of western Sweden. CT and MRI findings were classified from descriptive, local radiology reports and, if ambiguous, were reinterpreted by a neuroradiologist.

In the study from Victoria, MRI findings were classified by one of two paediatric radiologists, blinded to clinical information and imaging reports that had been generated previously. Although all available MRI scans were reviewed, the most recent good-quality scan was classified. Of the assessed scans, 6% were neonatal scans and 27% were performed in the first year of life. Scans with dual abnormalities (5%) were excluded. MRI was relatively less available for children born in the earlier years of the 1999–2006 cohort (MRI was unavailable for 22% of the 1999 cohort and 7% of the 2006 cohort), children born at less than 32 weeks' gestation (54% vs 73% for children born at 32 or more weeks' gestation), children functioning at GMFCS level I or II (64% vs 72% for GMFCS levels III–V), and for those with spastic diplegia and hemiplegia compared with quadriplegia (63% and 65% vs 74%).
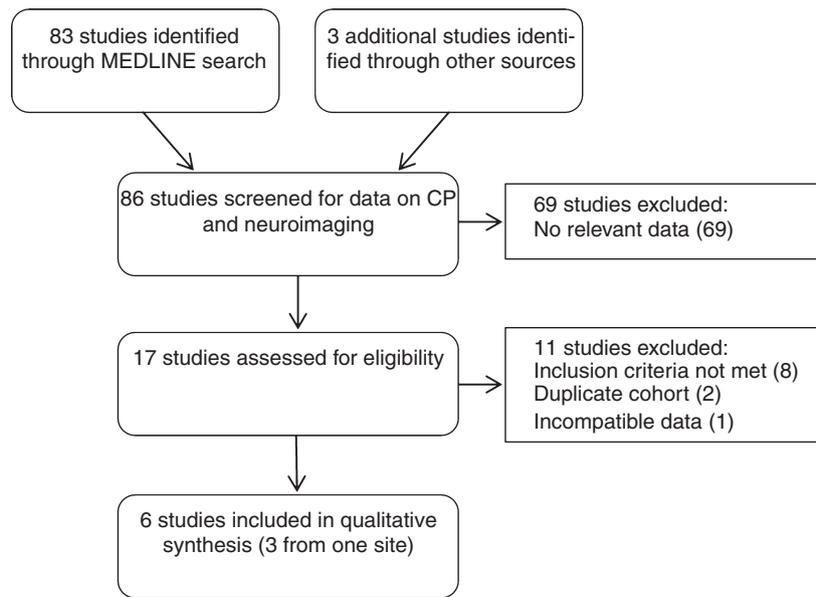
Figure 1: Flow diagram of the process used to select studies.

Table I: Details of the included population-based studies

Author	Year	Site	Years included	n	Imaging (%)	MRI (%)	CP subtypes	GMFCS	Term/preterm
Himmelmann et al.[9,a]	2005	Western Sweden	1995–1998	129	80	47	All		Both
Himmelmann et al.[19,a,b]	2010	Western Sweden	1999–2002	160	86	54	All		Both
Himmelmann and Uvebrant [20,b]	2011	Western Sweden	1999–2002	160	86	54	All	Yes	Both
Krägeloh-Mann and Horber[8]	1995	South-west Germany	1973–1986	56	11	100	BSCP		
Reid et al. [21,c]		Victoria, Australia	1999–2006	563	64	100	All	Yes	Both
Towsley et al.[16]	2011	Quebec, Canada	1999–2002	213	88	59	All	Yes	Both
Wu et al.[22]	2006	California, USA	1997–2002	78	81	71	Hemiplegia		

[a]Successive cohorts so data combined. [b]Same cohort. [c]Unpublished data. MRI, magnetic resonance imaging; CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; BSCP, bilateral spastic cerebral palsy.

Table III shows the distribution of imaging findings for all CP cases from the three studies. The proportions of malformations, focal vascular insults, and normal imaging were homogeneous between studies (I^2=0%), whereas heterogeneity was high for the proportions of WMI, GMI, and miscellaneous abnormalities (I^2=83–97%). Overall, the scans of 86% of 1065 children were deemed abnormal. WMI was detected in 19 to 45% of children, GMI in 14 to 22%, focal vascular insults in 10%, malformations in 11%, and miscellaneous abnormalities in 4 to 23%. There was no statistically significant difference between the proportions of children with each imaging pattern, based on whether the study included CT in addition to MRI.

Distribution of MRI patterns by time of birth

Data on imaging patterns for individuals born at term versus preterm were available from three CP registries, although two different cut-offs, 37 and 34 weeks, were used to differentiate term from preterm. The distribution of imaging patterns is presented separately for each cut-off

in Table IV, with data from Victoria and Sweden included in both. The proportion of each cohort born preterm was similar for the three included studies reporting a 37-week cut-off (36–40%),[16,19] and for the two studies using 34 weeks as the cut-off (21–25%).[9] Regardless of the gestational age at birth, estimates for the proportions of WMI were highly heterogeneous between studies, whereas the proportions of malformations and focal vascular insults were homogeneous. Estimates for the proportions of GMI showed high heterogeneity for children born preterm (using a 37-wks cut-off), but low heterogeneity for term-born children.

The proportion of scans showing no abnormality was 10 to 12% for preterm children and 14 to 15% for term-born or near term-born children, regardless of the gestational age grouping. WMI was diagnosed in 31 to 71% of children born at less than 37 weeks' gestation, and in 67 to 79% of children born before 34 wks' gestation. WMI was also identified in 12 to 32% of children born at 37 or more weeks' gestation and in 21 to 34% of those born at 34 or

Table II: Definitions/inclusions for imaging patterns from included studies

Imaging pattern	Definitions/inclusions
White matter injury	**Victoria:** Signal abnormality and/or volume loss in the periventricular and/or deep white matter. Ventricular dilatation, scalloping of the ventricles, and cysts may also be present **Quebec:** Abnormality/volume loss in the periventricular and/or deep white matter[16] **California:** Periventricular white matter lesions, intraventricular haemorrhage, periventricular venous infarction[21] **Germany:** Periventricular areas of signal hyperintensity on T2-weighted images (diffuse and mild signal increase was not taken into account)[20] **Sweden:** White matter lesions[9,19]
Grey matter injury	**Victoria:** Signal abnormality and/or volume loss predominantly involving the cortical–subcortical grey matter, deep grey matter, or both. White matter may also be involved **Quebec:** Subdivided into deep, superficial and diffuse GMI and defined as signal abnormality or volume loss in the basal ganglia/thalamus, cortical grey matter (typically associated with increase in ventricular volume) or globally/diffusely involving the cortex/subcortex, deep grey matter and subjacent white matter (i.e. ventricular enlargement)[16] **California:** Only one case of parasagittal watershed injury included[21] **Germany:** Included parasagittal brain injury, localized cortical necrosis, multicystic encephalomalacia, and basal ganglia injury[20] **Sweden:** Cortical–subcortical lesions, basal ganglia-thalamic lesions with or without additional parasagittal/hippocampal lesions[9,19]
Focal vascular insults	**Victoria:** Signal abnormality, volume loss, or porencephaly in an established vascular territory. Included venous sinus thrombosis and isolated haemorrhagic lesions **Quebec:** Labelled as cerebrovascular accident and defined as infarction in a specifically defined vascular territory[16] **California:** Arterial distribution ischaemic infarction and sinovenous thrombosis[21] **Germany:** None included[20] **Sweden:** Included as cortical/subcortical grey matter lesions[9,19]
Malformations	**Victoria:** Abnormal formation of the brain, including cortical dysplasia, polymicrogyria, lissencephaly, pachygyria, heterotopia, schizencephaly, cerebellar hypoplasia or dysgenesis, holoprosencephaly, hydranencephaly, hydrocephalus, and agenesis of the corpus callosum. This category also includes the sequelae of intrauterine infection, which may manifest as dystrophic, predominantly periventricular, calcification with or without focal white matter destruction, microcephaly, and cerebellar hypoplasia **Quebec:** Included cortical dysplasia, polymicrogyria, lissencephaly, pachygyria, heterotopias, schizencephaly, cerebellar hypoplasia or dysgenesis, holoprosencephaly, hydranencephaly, hydrocephalus, and agenesis of the corpus callosum. Infection defined as dystrophic, predominantly periventricular, calcifications with or without focal white matter destruction, and cerebral hypoplasia in conjunction with a known positive serology[16] **California:** Included polymicrogyria, schizencephaly, large heterotopia associated with callosal agenesis and multiple interhemispheric cysts, congenital hydrocephalus, agenesis of the corpus callosum with absent septum pellucidum, and diffuse calcifications attributed to congenital cytomegaloviral infection[21] **Germany:** Included polymicrogyria, schizencephaly, lissencephaly, Arnold–Chiari malformation, genetic myelin defect[20] **Sweden:** Maldevelopments[9,19]
Miscellaneous	**Victoria:** Abnormalities unable to be classified into one of the other patterns **Quebec:** Other unclassifiable changes on imaging, e.g. delayed myelination, widened Vichow–Robin spaces, non-specific ventricular enlargement. Epidural, subdural, intracranial, or intraparenchymal haemorrhages were added to this category[16] **California:** Included large congenital choroid plexus tumour and large tumour of upper cervical cord[21] **Germany:** Included ventricular enlargement[20] **Sweden:** Cerebellar haemorrhage and sequelae of congenital cerebral primitive neuroectodermal tumour[9,19]

Table III: Distribution of imaging patterns for all cerebral palsy cases from three population-based studies

Site	n	Normal, % (95% CI)	White matter injury, % (95% CI)	Grey matter injury, % (95% CI)	Focal vascular insult, % (95% CI)	Malformation, % (95% CI)	Miscellaneous, % (95% CI)
Quebec	213	13.1 (8.9–18.4)	19.2 (14.2–25.2)	22.1 (16.7–28.2)	11.7 (7.7–16.8)	11.3 (7.4–16.3)	22.5 (17.1–28.7)[a]
Sweden	289	15.9 (11.9–20.6)	31.5 (26.2–37.2)	36.3 (30.8–42.2)[b]	11.8 (8.3–16.0)	4.5 (2.4–7.6)	
Victoria	563	13.1 (10.5–16.2)	45.3 (41.1–49.5)	14.4 (11.6–17.6)	9.4 (7.1–12.1)	10.3 (7.9–13.1)	7.5 (5.4–10.0)
I^2 (%); p		0; 0.526	97; <0.001	83; 0.016	0; 0.362	0; 0.787	94; <0.001
Weighted mean	1065	13.8 (11.7–15.8)	–	–	9.9 (7.8–12.0)	10.9 (9.0–12.7)	–

[a]Five cases of intracranial haemorrhage and three cases of infection in the Quebec data were reclassified as miscellaneous. [b]Focal vascular insults included with grey matter injury in the Swedish data. CI, confidence interval.

more weeks' gestation. Children born at 37 or more weeks' gestation were more likely to have brain scans showing GMI (21% vs 4–20%), focal vascular insults (12% vs 5%), and malformations (13% vs 7%) than children who were born preterm. Children born before 34 weeks' gestation were even less likely to have these imaging patterns: GMI

was reported in 1%, focal vascular insults in 2%, and malformations in 3% of cases.

Distribution of MRI patterns by CP subtype

Data on the distribution of imaging patterns for at least one CP subtype were available from California and

Table IV: Distribution of imaging patterns by term or preterm birth using two gestational age cut-offs

Gestational age	n	% of cohort	Normal, % (95% CI)	White matter injury, % (95% CI)	Grey matter injury, % (95% CI)	Focal vascular insult, % (95% CI)	Malformation, % (95% CI)	Miscellaneous, [a]% (95% CI)
Preterm <37 w								
Quebec	83	39.7	14.5 (7.7–23.9)	31.3 (21.6–42.4)	20.5 (12.4–30.8)	7.2 (2.7–15.1)	7.2 (2.7–15.1)	19.3 (11.4–29.4)[a]
Sweden	50	38.8	8.0 (2.2–19.2)	54.0 (39.3–68.2)	28.0 (16.2–42.5)[b]	8.0 (2.2–19.2)	2.0 (0.1–10.6)	
Victoria	199	35.7	9.5 (5.8–14.5)	70.9 (64.0–77.1)	4.5 (2.1–8.4)	5.0 (2.4–9.0)	6.5 (3.5–10.9)	3.5 (1.4, 7.1)
I^2 (%); p			0; 0.435	95; <0.001	91; p=0.001	0; 0.497	0; 0.930	86; 0.001
Weighted mean	332	36.7	10.2 (6.9, 13.4)	–	–	5.5 (2.8, 8.2)	6.9 (4.1–9.6)	–
Term 37+w								
Quebec	126	60.3	11.9 (6.8, 18.9)	11.9 (6.8, 18.9)	23.8 (16.7, 32.2)	14.3 (8.7, 21.6)	15.9 (10.0, 23.4)	22.2 (15.3–30.5)[a]
Sweden	79	61.2	20.3 (12.0–30.8)	19.0 (11.0–29.4)	35.4 (25.0–47.0)[b]	13.9 (7.2–23.5)	11.4 (5.3–20.5)	
Victoria	358	64.3	14.8 (11.3–18.9)	31.8 (27.0–36.9)	20.1 (16.1–24.6)	11.7 (8.6–15.5)	12.3 (9.1–16.1)	9.2 (6.4–12.7)
I^2 (%); p			19; 0.290	93; <0.001	0; 0.395	0; 0.464	0; 0.610	81; 0.005
Weighted mean	563	62.2	14.6 (11.7–17.5)	–	21.0 (17.3–24.6)	12.3 (9.4–15.2)	13.2 (10.4–16.0)	–
Preterm <34 w								
Sweden	33	20.6	18.2 (7.0–35.5)	66.7 (48.2–82.0)	9.1 (1.9–24.3) [b]	6.1 (0.7–20.2)	0.0[a]	
Victoria	141	25.3	10.6 (6.1–16.9)	79.4 (71.8–85.8)	1.4 (0.2–5.0)	2.1 (0.4–6.1)	2.8 (0.8–7.1)	3.6 (1.2–8.1)
I^2 (%); p			36; 0.211	99; <0.001	–	–	0; 0.648	–
Weighted mean	174	24.1	11.6 (6.8–16.3)	–	–	–	3.1 (0.5–5.7)	–
Term 34+w								
Sweden	127	79.4	15.7 (9.9–23.3)	21.3 (14.5–29.4)	47.2 (38.3–56.3)[b]	13.4 (8.0–20.6)	2.4 (0.5–6.7)[a]	
Victoria	416	74.7	13.7 (10.5–17.4)	34.4 (29.8–39.2)	19.0 (15.3–23.1)	11.8 (8.8–15.3)	12.7 (9.7–16.3)	8.4 (5.9–11.5)
I^2 (%); p			0; 0.583	89; 0.002	–	–	0; 0.839	79; 0.028
Weighted mean	543	75.1	14.1 (11.2–7.1)	–	–	–	12.9 (10.0–15.7)	–

[a]Five cases of intracranial haemorrhage and three cases of infection were reclassified as miscellaneous in the Quebec data. [b]Focal vascular insults included with grey matter injuries in the Swedish data. CI, confidence interval.

Germany in addition to Quebec, Sweden, and Victoria (Table V).[9,16,22,23] No heterogeneity between studies was found for the proportions of focal vascular insults and malformations in children with each CP subtype (I^2=0%). Heterogeneity between studies was high (I^2>75%) for the proportions of WMI in children with all CP subtypes, except spastic quadriplegia and ataxia. On the other hand, estimates for the proportions of GMI showed high heterogeneity solely for children with spastic hemiplegia. In the population cohorts from California and Victoria, only 1% and 6% of children with hemiplegia had GMI respectively, compared with 20% in the Quebec cohort. Overall, heterogeneity was low to moderate for normal imaging (I^2<75%), and moderate to high for miscellaneous findings (I^2>50%).

Normal imaging was common in children with ataxic CP (24%–57%) and relatively uncommon in those with spastic quadriplegia (7%). Although WMI was common in children with all CP subtypes, children with spastic diplegia had the highest rate of WMI (31%–60%). In contrast, GMI was the most frequent imaging pattern in children with spastic quadriplegia (34%) and dyskinesia (21%). Focal vascular insults were seen predominantly in children with hemiplegia (24%), whereas malformations tended to be associated with ataxia (18%), quadriplegia (16%), and hemiplegia (13%). Miscellaneous findings were reported for children with all CP subtypes.

Distribution of MRI patterns by GMFCS level
Studies from Quebec, western Sweden, and Victoria included data on the distribution of imaging patterns for each GMFCS level (Table VI).[16,20] The proportion of children functioning at GMFCS levels III, IV, and V varied by 10% or less between cohorts, whereas the proportions for GMFCS levels I and II varied by between 16% and 23%. As a result, these two GMFCS levels were combined. The rates of focal vascular insults, malformations, and normal findings were mostly homogeneous between the three studies. Heterogeneity was at least moderate for WMI at all GMFCS levels, and for GMI in children functioning at GMFCS levels I to II.

Children functioning at GMFCS levels I to II tended to have high rates of normal imaging (17%) and focal vascular insults (14%), whereas only 7 to 8% of children functioning at GMFCS level IV or V had normal imaging and 4 to 5% had focal vascular insults. WMI was the most frequent pattern at all GMFCS levels, except for children in level V. Children functioning at level V were more likely than less severely affected children to have imaging showing GMI (36% vs 7%–22% for other levels) and malformations (18% vs 8–12% for other levels).

DISCUSSION
This review describes the degree of consistency between population-based studies in the proportions of normal neuroimaging and five abnormal neuroimaging patterns in children with CP. An important finding was that heterogeneity across studies is likely to be the result of methodological, rather than population, differences.

Issues around classification of imaging
It is reassuring that population CP registries are now using broadly comparable classification systems for imaging findings. This allowed us to assess the degree of consistency

Table V: Distribution of imaging patterns by cerebral palsy subtype

Cerebral palsy subtype	n	Normal,% (95% CI)	White matter injury,% (95% CI)	Grey matter injury,% (95% CI)	Focal vascular insult,% (95% CI)	Malformation,% (95% CI)	Miscellaneous[a],% (95% CI)
Spastic hemiplegia							
California	78	15.7 (8.9–25.0)	37.1 (27.1–48.0)	1.1 (0.0–6.1)	23.6 (15.2–33.8)	16.9 (9.9–26.3)	5.6 (1.8–12.6)
Sweden	60	13.3 (5.9–24.6)	45.0 (32.1–58.4)	28.3 (17.5–41.4)[b]	11.7 (4.8–22,6)	1.7 (0.0–8.9)	
Quebec	71	4.2 (0.9–11.9)	18.3 (10.1–29.3)	19.7 (11.2–30.9)	26.8 (16.9–38.6)	12.7 (6.0–22.7)	18.3 (10.1–29.3)
Victoria	184	8.2 (4.6–13.1)	47.3 (39.9–54.8)	6.0 (3.0–10.4)	23.9 (17.9–30.7)	12.5 (8.1–18.2)	2.1 (0.6–5.5)
I^2 (%); p		62; 0.047	88; <0.001	89; <0.001	0; 0.876	0; 0.777	78; 0.004
Weighted mean	404	–	–	–	24.4 (19.8–28.9)	13.2 (9.9–16.5)	–
Spastic diplegia							
Quebec	36	27.8 (14.2–45.2)	30.6 (16.3–48.1)	13.9 (4.7–29.5)	0.0	8.3 (1.8–22.5)	19.4 (8.2–36.0)
Victoria	167	19.2 (13.5–26.0)	59.9 (52.0–67.4)	6.6 (3.3–11.5)	1.2 (0.1–4.3)	4.8 (2.1–9.2)	8.4 (4.7–13.7)
I^2 (%); p		12; 0.286	91; 0.001	31; 0.230	0; 0.836	0; 0.474	60; 0.113
Weighted mean	203	20.4 (14.9–25.9)	–	7.3 (3.8–10.9)	1.2 (0.0–2.8)	5.2 (2.1–8.2)	–
Spastic quadriplegia							
Quebec	79	7.6 (2.8–15.8)	20.3 (12.0–30.8)	30.4 (20.5–41.8)	6.3 (2.1–14.2)	13.9 (7.2–23.5)	21.5 (13.1–32.2)
Victoria	123	6.5 (2.8–12.4)	27.6 (20.0–36.4)	36.6 (28.1–45.7)	4.9 (1.8–10.3)	17.1 (10.9–24.9)	7.3 (3.4–13.4)
I^2 (%); p		0; 0.767	31; 0.228	0; 0.359	0; 0.677	0; 0.536	87; 0.006
Weighted mean	202	6.9 (3.4–10.4)	24.4 (18.5–30.3)	34.0 (27.5–40.6)	5.4 (2.2–8.5)	15.7 (10.7–20.7)	–
Bilateral spasticity							
Germany	56	5.4 (1.1–14.9)	66.1 (52.2–78.2)	16.1 (7.6–28.3)	0.0	8.9 (3.0–19.6)	3.6 (0.4–12.3)
Sweden	63	19.0 (10.2–30.9)	31.7 (20.6–44.7)	34.9 (23.3–48.0)[b]	11.1 (4.6–21.6)	3.2 (0.4–11.0)	
Quebec	115	13.9 (8.2–21.6)	23.5 (16.1–32.3)	25.2 (17.6–34.2)	4.3 (1.4–9.9)	12.2 (6.8–19.6)	20.9 (13.9–29.4)
Victoria	290	13.8 (10.0–18.3)	46.2 (40.4–52.1)	19.3 (14.9–24.3)	2.8 (1.2–5.4)	10.0 (6.8–14.0)	7.9 (5.1–11.7)
I^2 (%); p		62; 0.048	93; 0.048	16; 0.306	0; 0.606	0; 0.900	84; 0.900
Weighted mean	524	–	–	20.1 (16.4–23.7)	3.0 (1.3–4.6)	10.4 (7.8–13.0)	–
All spasticity							
Sweden	123	16.3 (10.2–24.0)	38.2 (29.6–47.4)	31.7 (23.6–40.7)[b]	11.4 (6.4–18.4)	2.4 (0.5–7.0)	19.9 (14.4–26.4)
Quebec	186	10.2 (6.3–15.5)	21.5 (15.8–28.1)	23.1 (17.3–29.8)	12.9 (8.4–18.6)	12.4 (8.0–18.0)	
Victoria	474	11.6 (8.9–14.8)	46.6 (42.1–51.2)	14.1 (11.1–17.6)	11.0 (8.3–14.1)	11.0 (8.3–14.1)	5.7 (3.8–8.2)
I^2 (%); p		15; 0.306	95; <0.001	85; 0.010	0; 0.504	0; 0.883	93; <0.001
Weighted mean		11.8 (9.5–14.0)	–	–	11.5 (9.0–13.9)	11.4 (9.1–13.6)	–
Ataxia							
Sweden	7	57.1 (18.4–90.1)	0.0	14.3 (0.4–57.9)[b]	28.6 (3.7–71.0)	0.0	
Victoria	25	24.0 (9.4–45.1)	24.0 (9.4–45.1)	8.0 (1.0–26.0)	0.0	16.0 (4.5–36.1)	28.0 (12.1–49.4)
I^2 (%); p		61; 0.107	56; 0.129	–	–	0; 0.498	67; 0.081
Weighted mean		–	–	–	–	18.0 (4.8–31.2)	–
Dyskinesia							
Sweden	30	6.7 (0.1–22.1)	6.7 (0.1–22.1)	76.7 (57.7–90.1)[b]	10.0 (2.1–26.5)	0.0	
Quebec	15	26.7 (7.8–55.1)	6.7 (0.2–31.9)	13.3 (1.7–40.5)	0.0	0.0	53.3 (26.6–78.7)
Victoria	33	21.2 (9.0–38.9)	39.4 (22.9–57.9)	27.3 (13.3–45.5)	2.9 (0.1–14.9)	0.0	9.1 (1.9–24.3)
I^2 (%); p		57; 0.097	84; 0.002	30; 0.232	0; 0.754	0; 0.367	86; 0.001
Weighted mean		–	–	21.2 (9.8–32.6)	2.7 (0.0–8.2)	3.9 (0.0–10.6)	–

[a]Five cases of intracranial haemorrhage and three cases of infection were reclassified as miscellaneous in the Quebec data. [b]Focal vascular insults included with grey matter injuries in the Swedish data. CI, confidence interval.

between geographic cohorts in the definitions, methodologies, and distributions of imaging findings. GMI was less comparable between studies than the other categories investigated because the Swedish study included cerebral artery infarcts with GMI. Since risk factors and clinical outcomes are likely to differ between those children with mostly unilateral perinatal arterial ischaemic strokes and those with other, mostly bilateral, forms of GMI, we think there is merit in separating these groups. In the Quebec study, additional categories infection and intracranial haemorrhage-were used. We suggest that infection is an aetiological term that does not fit well with the other imaging categories. The small number of children with intracranial haemorrhage, inconsistent with the definitions of WMI or focal vascular insults, would suggest that these insults could be classified as miscellaneous.

In general, the proportions of focal vascular insults and malformations were consistently reported between studies. WMI was the pattern with the most heterogeneity.

Although the reported definitions of WMI appeared similar, differences in the distributions suggested that there was a lack of uniformity in its classification. Compared with Victoria, scans in the Quebec study were more likely to be classified as GMI or miscellaneous than WMI. The disparity between the two cohorts was particularly apparent for preterm children, children with hemiplegia, and children functioning at GMFCS levels I and II. The authors of the Quebec study suggested that this difference might be partly due to classification being based on clinical descriptions. We hypothesize an additional explanation for the observed differences that relates to the classification of scans showing intraventricular haemorrhage (IVH) and/or periventricular haemorrhagic venous infarction (PVHI). IVH and PVHI are more typically unilateral or grossly asymmetrical,[24,25] and some insults can result in severe ventricular dilatation and secondary hydrocephalus. IVH in preterm infants commonly arises in the region of the caudothalamic groove, where haemorrhage may not only

Table VI: Distribution of imaging patterns by Gross Motor Function Classification System level

GMFCS level	n	% of cohort	Normal, % (95% CI)	White matter injury, % (95% CI)	Grey matter injury, % (95% CI)	Focal vascular insult, % (95% CI)	Malformation, % (95% CI)	Miscellaneous, [a]% (95% CI)
I/II								
Quebec	108	50.7	13.9 (8.0–21.9)	22.2 (14.8–31.2)	15.7 (9.4–24.0)	16.7 (10.2–25.1)	12.0 (6.6–19.7)	19.4 (12.5–28.2)
Sweden	96	60.0	24.0 (15.8–33.7)	38.5 (28.8–49.0)	29.2 (20.3–39.3)[b]	7.3 (3.0–14.4)	1.0 (0.0–5.7)	
Victoria	324	58.8	16.0 (12.2–20.5)	49.7 (44.1–55.3)	7.4 (4.8–10.8)	13.9 (10.3–18.1)	7.7 (5.1–11.2)	5.2 (3.1–8.3)
I^2 (%); p			45; 0.163	94; <0.001	79; 0.029	0; 0.491	0; 0.427	92; <0.001
Weighted mean	528		16.6 (13.4–19.8)	–	–	14.5 (11.2–17.8)	8.2 (5.9–10.6)	–
III								
Quebec	28	13.1	17.9 (6.1–36.9)	25.0 (10.7–44.9)	25.0 (10.7–44.9)	7.1 (0.9–23.5)	3.6 (0.1–18.3)	21.4 (8.3–41.0)
Sweden	6	3.4	16.7 (0.4–64.1)	16.7 (0.4–64.1)	33.3 (4.3–77.7)[b]	0.0	33.3 (4.3–77.7)	
Victoria	71	12.9	12.7 (6.0–22.7)	43.7 (31.9–56.0)	15.5 (8.0–26.0)	1.4 (0.0–7.6)	9.9 (4.1–19.3)	16.9 (9.0–27.7)
I^2 (%); p			0; 0.806	61; 0.078	5; 0.304	21; 0.260	0; 0.410	0; 0.651
Weighted mean	105		14.0 (7.4–20.7)	–	17.6 (10.1–25.0)	1.8 (0.0–4.5)	6.6 (1.7–11.4)	18.6 (11.2–26.0)
IV								
Quebec	39	18.3	7.7 (1.6–20.9)	12.8 (4.3–27.4)	20.5 (9.3–36.5)	7.7 (1.6–20.9)	15.4 (5.9–30.5)	35.9 (21.2–52.8)
Sweden	19	11.3	0.0	42.1 (20.3–66.5)	31.6 (12.6–56.5)[b]	26.3 (9.1–51.2)	0.0	
Victoria	74	13.4	9.5 (3.9–18.5)	45.9 (34.3–57.9)	23.0 (14.0–34.2)	4.0 (0.8–11.4)	9.5 (3.9–18.5)	8.1 (3.0–16.8)
I^2 (%); p			0; 0.486	89; <0.001	0; 0.758	0; 0.445	31; 0.236	85; 0.001
Weighted mean	132		7.7 (2.8–12.6)	–	22.1 (14.4–29.7)	4.8 (0.9–8.8)	12.2 (6.7–17.7)	–
V								
Quebec	38	17.8	13.2 (4.4–28.1)	13.2 (4.4–28.1)	39.5 (24.0–56.6)	5.3 (0.6–17.7)	18.4 (7.7–34.3)	10.5 (2.9–24.8)
Sweden	39	22.0	5.1 (0.6–17.3)	7.7 (1.6–20.9)	69.2 (52.4–83.0)[b]	17.9 (7.5–33.5)	0.0	
Victoria	82	14.9	6.1 (2.0–13.7)	29.3 (19.7–40.4)	34.1 (24.0–45.4)	3.7 (0.8–10.3)	18.3 (10.6–28.4)	8.5 (3.5–16.8)
I^2 (%); p			0; 0.436	82; 0.004	0; 0.570	0; 0.701	0; 0.998	27; 0.253
Weighted mean	159		6.7 (2.8–10.6)	–	35.7 (27.2–44.3)	4.1 (0.6–7.6)	18.2 (12.2–24.2)	7.0 (2.5–11.6)

[a]Five cases of intracranial haemorrhage and three cases of infection were reclassified as miscellaneous in the Quebec data. [b]Focal vascular insults combined with grey matter injury in the Swedish data. GMFCS, Gross Motor Function Classification System; CI, confidence interval.

result in destruction of white matter and have secondary effects on cortical and thalamic development, but may also cause primary damage to the adjacent thalamus. On the other hand, classic periventricular leukomalacia (PVL) is typically bilateral and symmetrical,[25] and any secondary volume loss in the deep grey nuclei due to Wallerian degeneration along the affected white matter tracts may be more difficult to appreciate on qualitative assessment. In the classification system proposed by Krägeloh-Mann and Horber,[8] and in the data from both Victoria and California, WMI includes PVL, IVH, and PVHI. It is not clear that this is the case in the Quebec study. It is possible that only classic PVL was included as WMI, and that IVH and PVHI were included as either GMI, where grey matter was clearly involved, or as a miscellaneous finding where isolated ventricular dilatation was the finding on the assessed scan. This may partly explain the higher frequency of GMI and miscellaneous findings, particularly in children born preterm, who are particularly susceptible to IVH, and in those with hemiplegia, who are likely to have asymmetrical lesions. We recommend that the data of all children with evidence of previous PVL or IVH/PVHI be included under the category of WMI, and that isolated ventricular dilatation be included as a miscellaneous finding only if no earlier scans are available to differentiate the pathogenic mechanism.

Once further harmonization has been achieved, we suggest that the four abnormal imaging patterns in children with CP used for this review, in addition to categories for normal and miscellaneous findings, provide an optimum number of mutually exclusive and relevant groups for subgroup analysis in aetiological and epidemiological research. However, with adequate sample sizes, our understanding of causal pathways and structure–function relationships would be enhanced by further subgrouping. For instance, focal vascular injuries might be subdivided based on the arterial territories involved and/or the extent of involvement. Subclassifications of GMI have already been reported. The GMI pattern in the Krägeloh-Mann and Horber review[8] consisted of cortical or deep grey matter lesions, such as basal ganglia/thalamic lesions, parasagittal injury, and multicystic encephalomalacia. The Quebec study[16] subdivided GMI into deep, superficial, and diffuse forms. A scoring system for the severity of WMI in preterm infants is in current use neonatally,[26] but we are unaware of any classification of WMI relevant to later MRI or CT scans in children with CP.

The same methods were not used by all studies included in this review. The three MRI studies that included all CP cases used blinded classification, but, unlike the study from Victoria, in which original scans were assessed, the classifications used in the studies from Quebec and Sweden were made from radiology reports in which the original interpretations may not have been blinded to clinical history. When classifying imaging patterns, we suggest that blinding may not be necessary and that clinical history may, in fact, help differentiate the mechanisms behind, for example, isolated ventricular dilatation or diffuse cerebral atrophy. In the studies from Victoria and Quebec, preference was given to the most recent scan and no lower age limit was imposed. We believe it is ideal if all available scans are used to classify the primary imaging pattern.

Where assessment reveals more than one pattern that might explain the child's motor impairment, we recommend that these be excluded from the main dataset and be reported separately in future studies. In the study from Victoria, dual patterns were only noted in 5% of scans; this small percentage should make little difference to the distribution of imaging findings.

Normal neuroimaging

Our review suggests, based on evidence from three population-based cohorts, that MRI, or a combination of MRI and CT, identifies abnormality consistent with motor impairment in 86% of children with CP, using current imaging technologies and qualitative assessment methods.[9,16,19] This figure is slightly higher than the mean of 80% reported for MRI/CT and multiple forms of CP in the earlier 2008 review, but is similar to the 86% reported from MRI studies meeting the inclusion criteria for the 2007 review and the 88% for CT/MRI in population-based studies from the 2004 review.[2,3,8] No evidence was found to suggest that the proportion of children with normal imaging varied between broad gestational age groups. However, an increased likelihood of normal imaging was observed for children with ataxia compared with the other CP subtypes, and relatively fewer normal scans were found in children with spastic quadriplegia. Previous reviews reported slightly lower rates of normal imaging in children with hemiplegia relative to bilateral forms,[2,8] but quadriplegia was not differentiated from other CP subtypes. The reported proportions of normal imaging for children with dyskinetic CP were mixed, with high rates reported from Quebec and Victoria but low rates from Sweden. There was a trend towards lower rates of normal imaging for GMFCS levels IV and V compared with levels I and II.

A number of explanations have been proposed for normal imaging in CP. Two additional publications based on the Quebec and Victorian cohorts focused on normal imaging in CP,[27,28] and both sets of authors suggested that the limitations of contemporary imaging may be part of the explanation. In this context, Benini et al.[28] proposed a possible role for diffusion tensor imaging to assist in the detection of diffuse cerebral changes,[29] and functional MRI to investigate changes at the level of neuronal network connectivity or neurochemical signalling.[28,30] Metabolic and/or genetic causes have also been postulated as a possible explanation for normal imaging in some cases. In Victoria, Leonard et al.[27] performed metabolic testing in a subgroup of children with normal imaging and an inadequate explanation for their motor symptoms, but failed to make any new diagnoses. It is also possible that some cohorts included children who were wrongly diagnosed with CP, or who had slowly progressive conditions that masquerade as CP. In a Portuguese study involving 100 children, a review of clinical files revealed that 3 of 11 children with normal imaging did not meet the inclusion criteria for CP according to the Surveillance of Cerebral Palsy in Europe guidelines.[31]

Distribution of imaging patterns

This review presents population-based data on the distribution of imaging patterns for all CP cases and for specific subgroups, in addition to the overall proportion of abnormal findings. WMI was the most common imaging pattern for all children with CP, occurring in 19 to 45% of cases across three studies. Krägeloh-Mann and Horber[8] reported WMI in 56% of scans, but the results are not directly comparable since their review only included spastic–dyskinetic CP, and preterm children were over-represented in their review and under-represented in our review (52% vs 37% of the total cohort). On account of their increased susceptibility to WMI, it was not unexpected that 31 to 71% of children born preterm would have this pattern, but perhaps it is more surprising that the imaging of 12 to 32% of children born at term also showed WMI. In comparison, Krägeloh-Mann and Horber[8] reported WMI in 90% of preterm and 20% of term-born children. The true frequency, nature, and timing of WMI in term-born children are currently unclear.

WMI was found to be common in children with all spastic CP subtypes, although relatively more so in children with diplegia; this finding was also reported in the review by Krägeloh-Mann and Horber.[8] On the other hand, spastic quadriplegia was frequently associated with GMI, and hemiplegia with focal vascular insults. These findings have some credibility, since GMI has been observed following bilateral, severe hypoxic–ischaemic or metabolic insults,[32] and the most common focal vascular insults are unilateral arterial territory infarcts.[33] The distribution of imaging patterns for non-spastic motor types were heterogeneous, perhaps not only reflecting small samples, but also possible classification differences in assigning these motor types.[21] The Quebec, Swedish, and Victorian studies had available data on the distribution of imaging patterns by GMFCS level and all reported relatively high proportions of GMI and malformations at GMFCS level V, and high proportions of WMI and focal vascular insults at GMFCS levels I/II. This is the first review to present imaging findings by GMFCS level.

This study addresses some of the problems of imaging studies identified in the previous review by Korzeniewski et al.[2] First, only population-based studies were included in this review. Some studies were also able to identify where children with available imaging differed from those without imaging, so that imaging findings could be interpreted with this sampling bias in mind. Second, the study investigators had already classified and reported the findings of clinical scans in comparable, mutually exclusive categories. There were some classification differences, but harmonization of data into six pattern groups was possible with minimal reclassification. Third, the classification systems presented in this and the 2007 review from Krägeloh-Mann and Horber[8] were based on common pathogenic patterns of abnormality that do not imply specific aetiologies. Although each pattern may suggest associations with particular causal pathways, research is

needed to further elucidate the contribution of specific aetiologies to each brain imaging pattern. Fourth, no assumptions were made about the timing of the abnormalities seen on imaging. Although there is good evidence to suggest that malformations are of antenatal origin, we do not believe a clear rationale exists for the timing of the other patterns in general; however, serial imaging and clinical features may suggest the likely timing in individual cases. Finally, the imaging for studies included in this review was independently classified in Victoria, and reports were independently assessed in Quebec and Sweden.

This review, however, has some limitations. It is possible that some population studies were missed in the search process. Furthermore, the generalizability of our findings to all children with non-postneonatally acquired CP in developed countries may be limited by the availability of imaging data in only 64 to 88% of cases, and by the selective unavailability of neuroimaging in particular subgroups. The studies from Quebec and Victoria both found that fewer children born preterm, with spastic diplegia, and functioning at GMFCS levels I and II had available imaging. Since these characteristics are often associated with either WMI or normal imaging, and since all three studies included similar proportions of children born preterm, these two imaging patterns may have been under-reported in all included studies. Future reviews that include a greater number of population-based studies, and studies sampling a higher proportion of known CP cases, may yield results that are more generalizable to the entire CP population.

CONCLUSION

MRI currently detects abnormality in approximately 86% of children with CP; this conclusion is based on high-quality evidence from a small number of population studies. Although CP registries are now using comparable classification systems for imaging findings, further dialogue is recommended in order to resolve some inconsistencies, which were noted as part of this review. Achieving harmony around broad groups of imaging findings will open the door to future collaborations in which more detailed analysis can be undertaken of imaging patterns and their associations with relevant antecedent factors and clinical outcomes. Our ultimate aim is to increase our understanding of causal pathways in CP and identify opportunities for future preventative strategies.

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