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Full length article

## Isolated choroid plexus cysts and health and developmental outcomes in childhood and adolescence – A systematic review

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## ABSTRACT

**Objectives:** Choroid plexus cysts (CPCs) are incidental findings on ultrasound examination of the fetal brain. It is not known if isolated CPCs are associated with any adverse health or neurodevelopmental outcomes during the life course. This systematic review aimed to collate and synthesize the evidence on whether or not isolated choroid plexus cysts are associated with an increased risk of adverse health or developmental outcomes during childhood and adolescence.

**Methods:** A search strategy was developed specifically for this study and applied to four electronic databases Medline (Ovid), Embase (Ovid), Web of Science, and Google Scholar. Studies were assessed and selected for inclusion if there was a measurement of CPC (including single or multiple; unilateral or bilateral; isolated or presenting alongside other markers) during the antenatal or early neonatal period (<7 days) with follow-up of children and adolescents for health and developmental outcomes measured at any time from age 1 month onwards. Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale. Due to heterogeneity in the types of outcome measures included and the timing of measurement of outcomes across the studies, it was not possible to pool data across studies and a narrative description of findings was presented.

**Results:** Eight studies (three cohorts and five case series) met the inclusion criteria. Different methods were used for outcome assessment, such as in-person assessment, parent questionnaires, medical records, and telephone interviews with parents. Six studies measured outcomes only once during the specified duration of follow-up; two studies carried out paediatric reviews of the children several times during follow-up. There were no differences in developmental outcomes or physical health between babies with CPCs reported in the three cohort studies, and no abnormalities were detected in the children that were followed up in four of the five case series studies. Most of the included studies were graded as low quality due to the small sample size, high risk of selection bias, unclear definitions of CPC or lack of a comparison group.

**Conclusions:** The studies conducted to date do not provide evidence of adverse physical health outcomes or neurodevelopmental delays in babies with CPCs. However, most of these studies were small and included a narrow range of outcomes. Further research is needed to explore the relative incidence of outcomes such as ASD, ADHD, epilepsy and educational attainment in children with CPCs.

## Introduction

Choroid plexus cysts (CPCs) are pseudocysts that can appear in one or both lateral ventricles of the developing fetus in the choroid plexus [1]. During routine antenatal ultrasound scans, they are diagnosed in

around 1% of fetuses in the first and second trimesters of pregnancy [2,3]. CPCs are easily and routinely identified within the fetal cranium at the time of the detailed (“20 weeks”) ultrasound examination but may also be detected in early neonatal cranial ultrasound scans [4–6]. CPCs were first detected prenatally in 1984 [7,8] and it has been suggested

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that the formation of the cysts is related to the histogenesis of the choroid plexus of the lateral ventricles [9]. Although their cause is uncertain, they typically resolve in 94% of cases when a follow up scan is done in the third trimester [7]. There was thought to be an increased risk of aneuploidy, mainly trisomy 18, with CPCs detected during antenatal ultrasound screening, however in the majority of cases, the risk of developing aneuploidy and trisomy is small and increases with older maternal age [10]. In a recent study of 18,841 unselected singleton pregnancies at second trimester fetal anomaly screening, we detected 159 babies with CPCs, but there was no association with congenital anomalies, preterm births or small for gestational age [2]. Previously, a systematic review of outcomes associated with CPC detected during the neonatal period reported that whilst bilateral CPCs were associated with chromosomal abnormalities and congenital infections, unilateral CPCs were not [11]. There have been a few observational studies that examined the longer-term outcomes in children and adolescents associated with CPCs, whether these were detected during the antenatal or neonatal period. In this systematic review we aimed to summarise all observational data on the longer-term outcomes associated with isolated CPCs detected during antenatal or neonatal ultrasound scans. The detection of any findings on ultrasound examination is stressful for the mother and her family, particularly when there is uncertainty about the future implications for the health and development of the baby. Collation of the evidence base is therefore needed to support the counselling of parents following the detection of CPCs on ultrasound scans [12–17].

## Methods

The protocol was registered in PROSPERO (reference no. CRD42022352433) and results are reported in accordance with PRISMA guidelines [18]. Eligible articles were identified through keyword searches of four electronic databases: Medline (Ovid), Embase (Ovid), Web of Science, and Google Scholar (first 100 records) using search terms (“choroid plexus cyst\*” OR “choroid plexus”) AND (“development\* outcome\*” OR “postnatal outcome\*” OR “child\* development\*” OR “mental development\*” OR “cognitive development\*” OR “motor development\*” OR “autonomic development\*” OR “physical development\*” OR “development\* delay” OR “developmental disorder” OR “neurodevelopmental delay” OR “neurological abnormalities” OR “behavioral development\*” OR “adaptive behavior” OR speech OR language OR vision OR hearing OR “motor skill\*” OR intelligent\* OR “autism” OR “attention deficit disorder” OR epilepsy OR “brain diseases” OR “adolescent development\*”). No language or date of publication restrictions were imposed on the search. Duplicates were removed manually, and two reviewers screened the outputs of search results for eligibility. Studies were assessed and selected for inclusion according to the following criteria: measurement of CPC (including single or multiple; unilateral or bilateral; isolated or presenting alongside other markers) during the antenatal or early neonatal period (<7 days) with follow-up of children and adolescents for health and developmental outcomes measured at any time from age 1 month onwards. We included all observational studies as long as they fulfilled these criteria, regardless of whether or not there was a control group, to be as inclusive as possible of the studies that have examined this topic. This was a post-hoc decision and a change to the protocol registered on Prospero because there were so few studies that included a control group. We excluded studies that focused on chromosomal or congenital abnormalities as an outcome as these have been dealt with in previous systematic reviews.

## Outcome measures

We included any health (e.g. epilepsy) or developmental outcomes (physical, social and emotional, cognitive and speech and language) measured during childhood or adolescence (including behavioural or educational attainment). Developmental outcomes were measures

completed by parents (e.g. Ages and Stages (ASQ-3) or Parents’ Evaluation of Developmental Status (PEDS)), measures completed by health professionals with varying input from parents (e.g. Child Development Inventory, Bayley Scales of Infant and Toddler Development) or completed by health professionals (e.g. Mullen Scales of Early Learning, Battelle Developmental Inventory, Brigance Early Childhood Screens, Denver II, Griffiths Mental Development Scales-Extended revised, Schedule of Growing Skills –II).

## Data extraction and data synthesis

Titles/abstracts were screened and reviewed by two reviewers independently for eligibility. Disagreement was resolved by mutual consent and discussion, with final inclusion agreed by all authors. Data extraction was carried out using a form that was developed specifically for this study. Data were extracted by one researcher and cross checked by a second reviewer.

## Quality assessment

We used the Newcastle-Ottawa Quality Assessment Scale (NOS) to assess study quality of the included studies (Appendix 1) [19]. It consists of three domains: selection, comparability and outcome. Each answer was awarded a star, with a possible total of 4 stars for Selection, 2 stars for Comparability, and 3 stars for Outcomes. Studies that had <5 stars were graded as low quality, 5–7 stars as moderate quality, and ≥8 stars as high quality (Table 2). Quality assessment was conducted by two reviewers independently, with any discrepancies resolved through discussion with the study authors.

## Results

### Study selection

Our search identified 2430 articles (see Fig. 1). After removing duplicates, we screened 1981 articles based on their titles and abstracts and found 11 potentially eligible studies for which full text papers were retrieved. Of these, we excluded 3 because they were conference abstracts/proceedings with either insufficient data to enable assessment or they did not meet our inclusion criteria for outcome measures. Our review therefore consisted of 8 studies.

### Study characteristics

All eight studies included in the review were hospital based (see Table 1). Three were cohort studies that included a group of babies who had CPCs detected either in the antenatal or early neonatal period and a control group of babies with no CPCs detected; both groups were followed up for outcomes during childhood and adolescence [20–22]. The other five were case-series, where a group of babies with CPCs detected either during the antenatal or early neonatal period were followed up but there was no control group [4,23–26]. All studies included babies that were born after 35 weeks gestation. Three studies were conducted in Taiwan [4,21,24], two were in USA [20,26] and single studies in Turkey [23], Israel [25] & Canada [22]. The timing of exposure measurement varied between studies. Ultrasound scans were done during the second trimester in five studies [20,22,23,25,26], and in the early neonatal period in three studies [4,21,24]. Across the studies, a total of 14,723 pregnant women and 18,939 babies underwent and ultrasound scans, leading to the detection of CPC in 208 babies during the antenatal period and 493 babies during the early neonatal period. Length of follow-up varied between the studies ranging from 18 months to 15 years. Most studies measured outcomes only once during the specified duration of follow-up with the exception of two studies [21,23] in which paediatric reviews of the children were carried out several times during follow-up. Across the studies, different methods were used for outcome

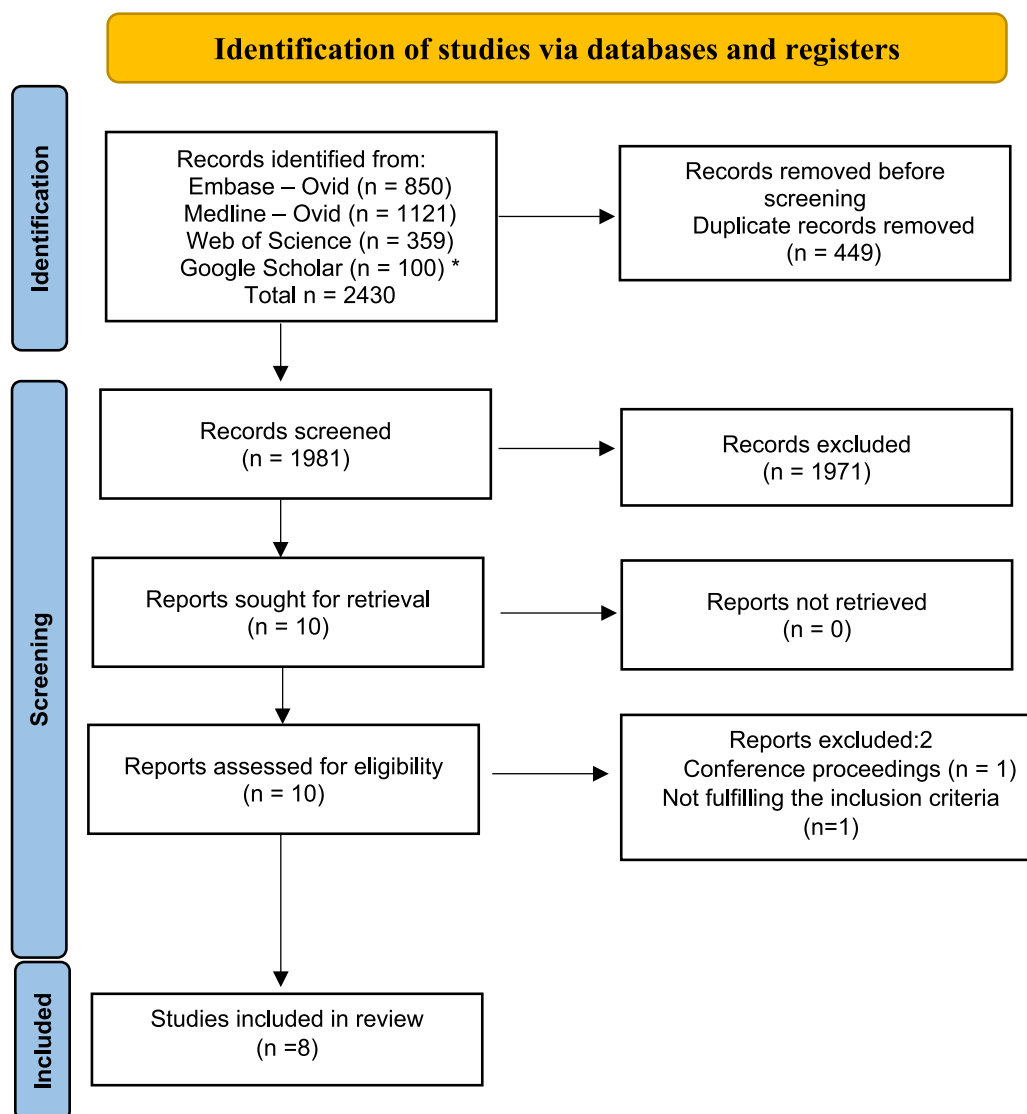


Fig. 1. PRISMA chart showing study selection process along with reasons for exclusion\* only first 100 records retrieved.

assessment such as in person assessment [20,22], parent questionnaire [20,22], medical records [23,24] and telephone interview with the parents [23,25,26].

In two of the three cohort studies, 155 pregnant women had ultrasound scans during the third trimester of pregnancy and CPC was detected in 62 babies [20,22]. Both of these studies used the Bayley Scales of Infant Development II, in addition to a number of other standardised tests for developmental outcomes [22] and physical health [20] at 18 months [20] and between 3 and 8 years [22] respectively. Overall, there were no differences in developmental outcomes or physical health reported between the CPC and control groups in both studies. In one of these studies the CPC group had statistically significant lower scores for verbal IQ and expressive language (Expressive One Word Picture Vocabulary Test) compared to controls, however these were not clinically significant, and the mean age of children in the CPC group was significantly lower (3.88 years (SD = 0.83) than in the control group (4.62 years (SD = 1.03) [22].

The third cohort study was conducted in Taiwan, where Cranial Ultrasound (CUS) examinations are available to normal, full-term neonates as a health examination item [21]. In this study, 5147 neonates underwent cranial ultrasounds during the first week of birth. CPC were detected in 23 neonates but there were no cases of developmental delay diagnosed in this group up to age 7 years. This compares with 245 cases

of developmental delay diagnosed in the group of 4898 neonates who had a normal cranial ultrasound scan.

Two studies used a case series design to report on CPC cases diagnosed during antenatal ultrasound scans undertaken in the second trimester [25,26]. In the first of these, 8270 women underwent second-trimester ultrasound examinations [26]. CPC were detected in 89 pregnancies and these mothers were offered fetal karyotyping, and followed with serial ultrasounds. Three of the 61 women who took up this offer had abnormal karyotypes (trisomy 18) identified, and they also had additional sonographic abnormalities. The remaining 28 women who chose not to undergo fetal karyotypic analysis delivered phenotypically normal infants. Infant and childhood developmental follow-up was performed on 76 children between 12 and 82 months; no abnormalities were detected using a modified Denver II Developmental Screening Test. In the second case series study, 6220 women had second-trimester ultrasound scans and 27 cases of isolated CPCs were detected. These children were followed up by paediatricians between 3 months to 3 years using a telephone interview with parents to assess neurodevelopmental development and suboptimal development was reported in two cases.

The other two case series studies were carried out in Taiwan [4,24]. Across these studies, 2111 [4] and 11,681 [24] neonates had a cranial ultrasound scan during the first week of life and CPC were detected in

**Table 1**  
Characteristics of studies included in the systematic review.

Author, Year, Country Study Recruitment period	Study design	Exclusions	Timing of exposure measurement	No. pregnant women/ neonates scanned	No. of CPC cases	Maximum length of follow up	Age at outcome measurement	Outcome Measures	Outcome assessment method	Interpretation of results
Bernier, F. et al. (2005) [22] Canada January 1993 - December 1998	Retrospective cohort	Assess abnormality detected either prenatally or postnatally, multiple gestations, one or more major malformation(s) detected prenatally or postnatally or those children whose primary language was not English.	2nd trimester	85	37	96 months	CPC group: 2.7–6.8 years Control group: 2.3–8.3 years	Bayley Scales of Infant Development II, ANSER, WPPSI-R, WISC-III, PPVT-III, CELF-R, Stanford-Binet Verbal Absurdities, M-ABC, VABS	in-person assessment, parent questionnaire	There were no significant group differences in Full-Scale IQ (FSIQ) or Performance IQ (PIQ). However, Verbal IQ was slightly lower in the CPC group compared to controls ( $p < 0.05$ ). Additionally, children in the CPC group scored lower on EOWPVT but higher on the Vineland socialization domain compared to the control group.
DiPietro, J. et al. (2011) [20] USA 2 years (dates not specified)	Cohort	Abnormal ultrasound findings in addition to CPC, high risk pregnancies, smokers, multiple pregnancies	2nd trimester	Total number of pregnant women scanned not specified	118 CPC cases identified 31 were included in the study and 25 were include in the analysis	18 months	16.2 to 21.2 months	Bayley Scales of Infant Development II, motor activity and energy expenditure using accelerometers, autonomic control of the heart and vagal tone using ECG.	in-person assessment, parent questionnaire	There were no significant differences were reported developmental variables for cases and controls.
Tosun, M et al. (2019) [23] Turkey Between January 2005 and January 2010	Case series		15–22 weeks	Total number of pregnant women scanned not specified	14 isolated bilateral CPC and 12 isolated unilateral CPC	8 years	4 – 8 years	Neurodevelopmental disorders and physical impairments	Follow up by paediatricians and review of medical records and parent interviews	Epilepsy and Attention-deficit/hyperactivity disorder (ADHD) were diagnosed in two liveborn with BCPC but unclear as to whether or not these children also had other soft markers.
Chang, H. et al. (2019) [21] Taiwan Between July 2002 and December 2012	Retrospective cohort	Neonates with dysmorphism or underlying neurologic problems suspected by pediatric neurologist who were later confirmed to have congenital infections, chromosomal abnormalities, genetic or neuromuscular disorder	1st week of birth	5147	23	15 years	0 – 2 months 2–4 months, 4 – 10 months, 10 – 18 months, 18–24 months, 24 – 36 months, 36 – 83 months.	Neurodevelopmental disorder diagnosis (ICD-9) Diagnostic criteria of Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition (DSM-IV) for ADHD and ASD	in-person assessment	No cases of developmental delay were observed in the children with CPC.
Hung, K. and Liao, H. (2002) [4] Taiwan Between July 1997 to June 1998	Case series	None specified	First 3 days of life	2111	186	42 months	30 to 42 months	Denver II Developmental Screening Test (standard and modified)	in-person assessment & telephone survey	Normal early childhood development was observed for all 179 children as determined by the Denver II Developmental Screening Test

(continued on next page)

Table 1 (continued)

Author, Year, Country Study Recruitment period	Study design	Exclusions	Timing of exposure measurement	No. pregnant women/ neonates scanned	No. of CPC cases	Maximum length of follow up	Age at outcome measurement	Outcome Measures	Outcome assessment method	Interpretation of results
Lin, Y. et al. (2004) [24] Taiwan Between October 2011 and October 2018	Cohort/case series	Neonates admitted to the newborn center or intensive care unit within 24 h after birth or those who underwent examination 7 days after birth were excluded	First 7 days after birth	11,681	284	7.8 years	1 to 7.8 years	Neurodevelopmental disorder diagnosis (DSM-5), ADHD and ASD diagnosed by a pediatric psychiatrist using psychological assessments and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition	medical records	ADHD in 3 cases of CPC
Digiovanni, L. et al. (1997) [26] USA, January 1990 through August 1995	Cohort/case series	None specified	18.2 ± 1.9 weeks	8270	89	82 months	12–82 months	Denver II Developmental Screening Test (modified)	telephone interview with parent	Among the 89 fetuses with prenatally diagnosed CPC, three had trisomy 18 and other abnormalities on the ultrasound scan. Normal early childhood development, as determined by the modified Denver II Developmental Screening Test
Leitner, Y. et al. (2004) [25] Israel, Between 1994 and 1999	Cohort/case series	None specified	15–41 weeks	6220	27	3 years	3 months – 3 years	Neurodevelopmental delay assessment – method not specified	telephone interview with parent	Suboptimal neurodevelopmental outcome in 2 cases of isolated CPC.

CPC-Choroid plexus cysts.

ANSER-Aggregate Neurobehavioral Student Health and Educational Review.

WPPSI-R -Wechsler Preschool and Primary Scale of Intelligence—Revised.

PPVT-III- Peabody Picture Vocabulary Test—III.

CELF-R- Clinical Evaluations of Language Fundamentals—Revised.

VABS- Vineland Adaptive Behaviour Scales.

M-ABC-Movement Assessment Battery for Children.

EOWPVT-Expressive One Word Picture Vocabulary Test.

ECG-Electrocardiogram.

ADHD- Attention-Deficit/Hyperactivity Disorder.

**Table 2**  
Quality assessment of included studies.

Study	Selection criteria				Comparability of Cohorts based on the Design or Analysis	Outcome			Total Score
	Representativeness of the Exposed Cohort	Selection of the unexposed Cohort	Ascertainment of Exposure	Demonstration that outcome of interest was not present at start of study		Assessment of Outcome	Was Follow-up Long Enough for Outcomes to Occur	Adequacy of Follow-up of Cohorts	
Bernier, F. et al. (2005) [22]	–	*	–	*	*	–	*	–	4
DiPietro, J. et al. (2011) [20]	–	*	–	*	**	*	*	*	6
Tosun, M. et al. (2019) [23]	–	–	–	*	–	–	*	–	2
Chang, H. et al. (2019) [21]	–	*	*	*	*	–	*	*	6
Hung, K. et al (2002) [4]	–	–	–	*	–	–	*	*	3
Lin, Y. et al. (2004) [24]	–	*	–	*	–	–	*	*	4
Digiovanni, L. et al. (1997) [26]	–	–	*	*	–	–	*	*	4
Leitner, Y. et al. (2004) [25]	–	–	*	*	–	–	*	*	4

\*Each asterisk represents whether individual criteria within the subsection was fulfilled.

186 and 284 babies respectively [4,24]. These babies had their development assessed by paediatricians. All the 179 babies who completed follow-up in one study had normal development [4], while in the other study 3 babies with CPC were diagnosed with ADHD [24].

The results of the quality appraisal, using the Newcastle Ottawa scale, is presented in Table 1 [19]. Out of eight studies, only two were of moderate quality [20–22]. The remaining six studies were of low quality due to small sample size, lack of precise definition of CPC or lack of a comparison group. For example, one study [20] had a high risk of selection bias as it was not clear what criteria were used to invite women to participate and in another study [24] participants were neonates whose parents had opted to self-pay for cranial ultrasound screening, thus excluding participants who may not have had the resources to do this.

## Discussion

To our knowledge this is the first systematic review that collates the evidence base on longer term outcomes associated with finding a CPC either during the antenatal or early neonatal period. We have focussed on isolated CPC findings as it is well documented that babies with multiple abnormalities are at higher risk of abnormal karyotypes and congenital anomalies. We found that there was a lack of evidence to support or refute the hypothesis that CPCs are associated with adverse health or neurodevelopmental outcomes, due to a small number of studies that were mostly of poor quality.

Our review identified two cohort studies [20,22] that measured CPC during the second trimester and neither of these detected clinically significant differences in neurodevelopmental outcome between babies in the CPC and control groups. Despite this, Bernier et al have suggested that there is a possibility that CPCs are associated with a risk of verbal

learning problems, as they found a trend for more children to display a discrepancy between verbal and nonverbal skills in the CPC group [22]. A third cohort study examined the incidence of neurodevelopmental disorders among babies who had a cranial ultrasound examination during the early neonatal period and found no cases with this outcome in CPC group [21]. There were five case series studies, three [23,25,26] of which included CPC cases diagnosed during the antenatal period; all of the isolated cases of CPC had normal neurodevelopment in one study [26], the other study [25] reported suboptimal neurodevelopment on two cases with isolated CPC. However, in the former study the Denver Developmental Screening Test II (Denver II) was administered by phone rather than by observation by a trained tester [26]. In the latter study it was not clear what criteria were used to make this diagnosis [25]. The third case series of antenatal diagnosed CPCs reported diagnoses of epilepsy and ADHD in two babies with CPC but it was not clear if these were isolated CPCs or if there were also other abnormalities present at the time of the ultrasound scan [23].

Using the hierarchy of evidence, cohort studies would usually take precedence over case series as cohort studies allow for the incidence of outcome in the exposed group to be compared with that in the unexposed groups and a summary measure of effect such as a relative risk to be calculated [27,28]. However, given the small number of cohort studies and limited range of outcomes studies, we took the decision to also include case series studies in this review. Overall, the quality of studies was low, with a number of studies judged as having a high risk of selection bias and attrition bias. In addition, sample sizes included were small, and therefore studies were likely to be underpowered to detect an association with adverse outcomes. In addition, few studies provided a clear definition of CPCs.

Ultrasound screening during the second trimester of pregnancy is common practice in most countries including the U.K, U.S.A and Canada

with the aim of detecting structural anomalies. It usually at this scan that ‘markers’ such as CPCs are also identified, and its significance for childhood development and health in later life in the absence of other abnormalities is not known. Whilst the studies included in this review suggest there is little evidence that isolated CPCs are associated with neurodevelopmental delay or disorders during childhood, the range of outcomes studied are limited and longer term behavioural and educational outcomes have not been studied. These longer term outcomes are important as there is a growing interest in understanding choroid plexus morphology in autism and other neurodevelopment disorders [29–31]. By contrast, in Taiwan, ultrasound screening during the neonatal period is used widely in clinical paediatrics for an immediate and non-invasive bedside examination of preterm neonates, who are at high risk of intracranial lesion, such as intracranial hemorrhage or post hypoxic cerebral damage [21]. Chang et al also report that CUS examinations have recently been extended to normal, full-term neonates as a health examination item in Taiwan. This is attributed to the decline in birth rate and parental concern about their infants health leading to an increase in the use of self-paid sonographies, including a CUS examination, for normal full-term neonates. The evidence from the studies included in this review suggests that the prevalence of CPCs on ultrasound scans in the neonatal period is low; there was no evidence of any association with neurodevelopmental delay in the studies included in this review.

### Strengths and limitations

We used a broad definition of CPCs to ensure that we included all possible evidence and evidence on CPCs with different features (single vs multiple; unilateral or bilateral) and a variety of health and developmental outcomes. However, the numbers of cases were too small to permit robust assessment of outcomes within these sub-categories. One of the limitations of the present review was that we didn’t include grey literature, so may have missed unpublished research such as analyses included in reports written by screening programmes.

### Conclusion

There is insufficient evidence of the neurodevelopmental outcomes associated with isolated CPC detected during the antenatal or early neonatal period. The available evidence suggests that there is no increased risk of adverse health outcomes or neurodevelopmental delay. However, this is based on data from very small studies that may have been underpowered to detect small differences between babies who had CPCs and those that did not. Whilst outcomes such as ASD and ADHD have been included in some case series, further research is needed, in the form of large high-quality cohort studies to explore the relative incidence of these outcomes in children who had isolated CPCs diagnosed in the antenatal period compared to those who did not. This could potentially be achieved using routinely available population based of obstetric datasets record-linked with child development, health service and educational datasets.

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### Ethical approval

Not required.

### Consent for publication

Not required as the manuscript doesn’t contain any individual person’s data in any form.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejogrb.2023.09.013>.

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