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A Systematic Review with a Meta-Analysis of the Morphological Variants of the Corpus Callosum: Related Neurocognitive Clinical Implications

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Key words
- Anatomical variation
- Anatomy
- Corpus callosum agenesis
- Corpus callosum
- Corpus callosum hypoplasia

Abbreviations and Acronyms
AQUA: Anatomical Quality Assessment
CC: Corpus callosum
CCA: Corpus callosum agenesis
CCCA: Corpus callosum complete agenesis
CCH: Corpus callosum hypoplasia
CI: Confidence interval
CNS: Central nervous system
LFK: Luis Furuya-Kanamori
MRI: Magnetic resonance imaging
US: Ultrasound

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BACKGROUND: **Corpus callosum agenesis (CCA) occurs in approximately 1 in every 4000 births and is identified in 3–5% of individuals evaluated through neuroimaging for neurodevelopmental disorders. The combined prevalence of CCA and hypoplasia is estimated to range from 1.8 to 10 in every 10,000 births.**

METHODS: **The online databases Medline, Scopus, Web of Science, Google Scholar, Cumulative Index to Nursing and Allied Health Literature, and Latin American and Caribbean Literature in Health Sciences were searched until May 2025. Two authors independently conducted the search, selected the studies, and extracted the data. The methodological quality of the studies was assessed using the Anatomical Quality Assessment tool. A random effects model was used to estimate the pooled prevalence.**

RESULTS: **A total of 46 studies met the established selection criteria. In this analysis, 15 articles were included in the meta-analysis, which involved a total of 5,118,037 subjects. The overall prevalence of CCA was 18% (confidence interval = 10%–25%). The subgroup analysis revealed a significant difference in the prevalence of CCA among the Asian continent compared to the other four continents (*P*-value 0.001).**

CONCLUSIONS: **Early diagnosis of CCA during the fetal stage can enable specialists to implement more effective treatments and reduce the likelihood of neurofunctional impairments. Furthermore, understanding the morphological characteristics of CCA can assist in making an early and accurate diagnosis, minimizing the need for differential diagnoses that could interfere with the functioning of the interhemispheric connection system and brain functional connections.**

INTRODUCTION

Corpus callosum agenesis (CCA) is a congenital disorder characterized by the partial or complete absence of the corpus callosum (CC).[1] This condition may occur in isolation or conjunction with other neurological and systemic abnormalities. Corpus callosum complete agenesis (CCCA) is classified when no portions of the CC are formed, while the development of only one portion characterizes partial corpus callosum agenesis. The severity of CCA can range from a total lack of structure to hypoplasia (corpus callosum hypoplasia [CCH]), in which the CC is underdeveloped.[2]

The development of the CC commences around day 74 of gestation and reaches completion by day 115; however, the myelination process continues postnatally.[3] During its development, the CC is constructed from the commissural plaque, a dorsal region of the telencephalon. In this region, pyramidal neurons from cortical layer III extend their axons, which cross the midline.[4] This process is critical for establishing interhemispheric connections, thereby facilitating the integration of sensory

and motor information between the cerebral hemispheres. The condition known as CCCA occurs in approximately 1 in 4000 births and is identified in 3%–5% of individuals assessed through neuroimaging for neurodevelopmental disorders. Furthermore, the combined prevalence of CCA and CCH is estimated to range between 1.8 and 10 per 10,000 births. These data underscore the rarity of the condition, which accentuates the significance of early detection and diagnosis for facilitating timely intervention.[5]

The clinical impact of CCA varies, manifesting as neuropsychological and social issues.[6] Individuals with isolated CCA and normal intellectual functioning have a more favorable prognosis but face distinctive neuropsychological and psychosocial challenges that disrupt daily life, including difficulties in problem-solving, pragmatic language, communication, and overall development.[7] CCA is linked to neurological dysfunctions, such as epilepsy and structural abnormalities like hydrocephalus and cysts.[8] Individuals with CCA may experience learning and memory challenges, especially with tasks integrating verbal and visual information. The severity and nature of these difficulties vary based on whether the agenesis is complete or partial and the presence of other neurological conditions.[9] In clinical management, prenatal ultrasound (US) and magnetic resonance imaging (MRI) are essential tools. These techniques allow for a thorough evaluation of brain development and identification of associated deformities. MRI provides detailed images that complement US findings, aiding postsurgery care planning.[9]

This systematic review, accompanied by a meta-analysis, sought to identify the scientific evidence concerning the morphological variants of the CC and their relationship to the clinical implications associated with the central nervous system (CNS).

METHODS

Protocol and Registration

The Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020 statement[10] guided the systematic review. The registration number in the Systematic Reviews Registry (PROSPERO) is CRD42024574548.

Electronic Search

In January, we searched several online databases to ensure we included the most relevant studies for our research question. These databases included MEDLINE (via PubMed), Google Scholar, Web of Science, Cumulative Index to Nursing and Allied Health Literature, Latin American and Caribbean Literature in Health Sciences, and Scopus, covering publications from their inception until December 2024. Our search strategy involved combining the following terms: "*variations of the corpus callosum*" (excluding MeSH), "*agenesis of the corpus callosum*" (excluding MeSH), "*partial agenesis of the corpus callosum*" (excluding MeSH), "*anatomical variations*" (excluding MeSH), "*clinical anatomy*" (excluding MeSH), and "*aberrant anatomy*" (excluding MeSH). We used the Boolean operators AND, OR, and NOT in this process (**Supplementary Table 1**).

Eligibility Criteria

The present systematic review included studies that examined the association between CC morphological variants and various clinical conditions. To be eligible for inclusion, the studies need to meet the following criteria: 1) they must involve dissections or imaging identifying the presence of CC morphological variants; 2) they should report on the prevalence of subjects with callosum corpus variants and their correlation with brain pathologies; and 3) only research articles were considered, including retrospective and prospective observational studies, published in English in peer-reviewed journals and indexed in the relevant databases. As exclusion criteria, we used the following to eliminate items from our selection: 1) sample: studies carried out in animals; 2) studies that analyzed variants of the region or system of CC; 3) we have not included variants of the vascularization of the CC since, although they may be present, they are not associated with agenesis; they can change the irrigation pattern but not the clinical condition; and 4) studies including letters to the editor, comments, or case reports.

Study Selection

Three authors conducted independent analyses to select studies thoroughly. Two authors (Valenzuela, J.J. and Orellana, S.) initially reviewed the titles and abstracts of references retrieved from the database searches. The full texts of these references were obtained for the studies they deemed potentially relevant. If the 2 reviewers could not reach a consensus, a third reviewer (Orellana M.) was involved in the decision-making process. Additionally, we performed an agreement test among the authors using the kappa statistic to evaluate reliability and the risk of bias among the reviewers. The calculated kappa value was 0.85, indicating good agreement.

Data Collection Process

Two authors (Nova P. and Sanchis J.) independently extracted data on the outcomes of each study. The following information was collected from the included studies: 1) authors and year of publication, 2) geographical region, 3) age and sex of participants, 4) sample size and prevalence, 5) symptoms, 6) contextual circumstances, 7) characteristics of variants, and 8) clinical considerations.

Assessment of the Methodological Quality of the Included Studies

To assess the bias of the included studies, we used the verification table for anatomical studies (Anatomical Quality Assessment [AQUA]) proposed by the International Working Group on Evidence-Based Anatomy (Henry et al. 2016). Two reviewers (Valenzuela J.J. and Nova P.) independently analyzed the 5 domains outlined by the AQUA tool. After their evaluations, they reached a consensus and created the table and the bias graph. Publication bias was assessed using the DOI plot and Luis Furuya-Kanamori (LFK) index.3.0 LFK index within ± 1 indicated no asymmetry, LFK index exceeds ± 1 but within ± 2 indicated minor asymmetry, and LFK index exceeds ± 2 indicated major asymmetry. To analyze publication bias and heterogeneity among the included studies, we used a funnel plot analysis. This analysis visualizes the relationship between each study's effect size and its precision, helping to identify unpublished studies

due to nonsignificant results in relation to the proportion of CCA.

Statistical Methods

The data extracted from the meta-analysis were analyzed using Jamovi software (accessed in October 2024) to calculate the prevalence of CC morphological variants. The DerSimonian-Laird model, along with a Freeman-Tukey double arcsine transformation, was used to combine the summary data. A random effects model was implemented due to the high heterogeneity observed in the prevalence data of CCA. To assess the degree of heterogeneity among the included studies, we used the χ^2 test and the I^2 statistic. For the χ^2 test, a P value of 0.10 was considered significant, as suggested by the Cochrane collaboration. The values of the I^2 statistic were interpreted with a 95% confidence interval (CI) as follows: 0%–40% indicates no significant heterogeneity, 30%–60% suggests moderate heterogeneity, 50%–90% reflects substantial heterogeneity, and 75%–100% denotes a considerable amount of heterogeneity.

Sensitivity Analysis

Sensitivity analysis by data exclusion is a statistical test that eliminates confounding variables, variables that may underestimate or overestimate the data. In this study, we performed 2 sensitivity analysis tests: the first was to eliminate studies with a prevalence greater than 50% and the second was to eliminate studies with a number greater than 10,000 subjects, which allows us to identify influential points and validate the robustness of the conclusions.

Subgroup Analysis

To avoid bias in estimating the differences in results between the subgroups of CC morphological variants, we conducted the same statistical analysis for these subgroups. Additionally, we included the prevalence of each subgroup and carried out qualitative assessments regarding clinical considerations. The subgroups were classified into imaging samples, fetuses, and cadaveric samples. We also categorized them based on geographical regions, CC morphological variants, and subgroups consisting of male and female participants, with each group analyzed individually.[11,12]

Description of the Corpus Callosum Morphological Variants

The brain has 2 hemispheres, right and left, connected by the CC. The cerebral cortex's outer layer features folds called gyri and grooves known as sulci. It is divided into 4 lobes: frontal, parietal, temporal, and occipital. The cerebrum also contains ventricles; 2 lateral ventricles are the largest, communicating with the third ventricle through the foramen of Monro. The third ventricle is in the midline, between the thalamus halves. The fourth ventricle is located in the brainstem, near the cerebellum, connecting to the third via the aqueduct of Sylvius, facilitating cerebrospinal fluid circulation (**Figure 1**). The brainstem, located caudally, connects the brain and spinal cord. It has 3 parts: the midbrain, the pons, and the medulla oblongata. The cerebellum and limbic system are also important; the limbic system includes the hippocampus, amygdala, hypothalamus, and cingulate gyrus. The hypothalamus regulates hunger, thirst, sleep, body temperature, and hormone secretion via the pituitary gland. The thalamus relays most sensory information to the cerebral cortex.[13-15]

The development of the CC begins around day 74 of gestation and is completed by day 115, although the myelination process continues after birth. During fetal development, the CC is formed from commissural plaque, a dorsal region of the telencephalon, where pyramidal neurons from cortical layer III extend their axons, crossing the midline. This process is crucial for establishing interhemispheric connections and facilitating sensory and motor integration between the cerebral hemispheres.

CC can be classified into 4 main parts: rostrum, genu, body, and splenium. There are also 3 types of CCA.

1. A decrease in size without morphological changes occurs when the CC is smaller but maintains its shape.
2. The "Apple Core CCA" is characterized by the hypoplasia of the posterior portion.
3. The "Anterior Remnant CCA" involves the agenesis of the middle and posterior portions, leaving only a small anterior remnant.

On the other hand, corpus callosum dysplasia involves abnormal formation and includes the "Hump-Shape CC" subtype, where hypoplasia is absent. CCH and corpus callosum dysplasia can overlap, leading to 2 additional classifications.

1. "Stripe CCA" features a uniformly thinner CC with dysplasia.
2. "Kinked CCA," characterized by deformation and torsion accompanied by hypoplasia.

CCA is defined as the total absence of this structure[16] (**Figure 2**).

Corpus Callosum Partial Agenesis. The CCPA is a congenital malformation; the structure that connects the 2 brain hemispheres is partially developed. Some segments of the CC, namely the genu (anterior part), body (middle part), rostrum, and splenium (posterior part), may be absent or not fully developed. A condition called batwing may occur, in which the horns of the ventricle take on a parallel rather than a convergent shape. The interhemispheric fissure tends to be more expansive than usual and can be associated with white matter and cortical alterations. Finally, the other cerebral structures are typical, as described in the brain anatomy.[4,17,18]

Corpus Callosum Complete Agenesis. CCCA results in a total lack of direct connection between the 2 hemispheres, which affects the transfer of information between the 2 sides of the brain. There are Probst bundle fibers; these nerve axons are oriented longitudinally along the hemisphere since they cannot reach the other hemisphere. This condition may produce ventriculomegaly of the lateral ventricles due to the nonappearance of the CC, which would cause a lack of supportive structure.[2,19-25]

RESULTS

Selection of Articles

The search yielded 1378 articles from various databases that met our research team's criteria and search terms. We

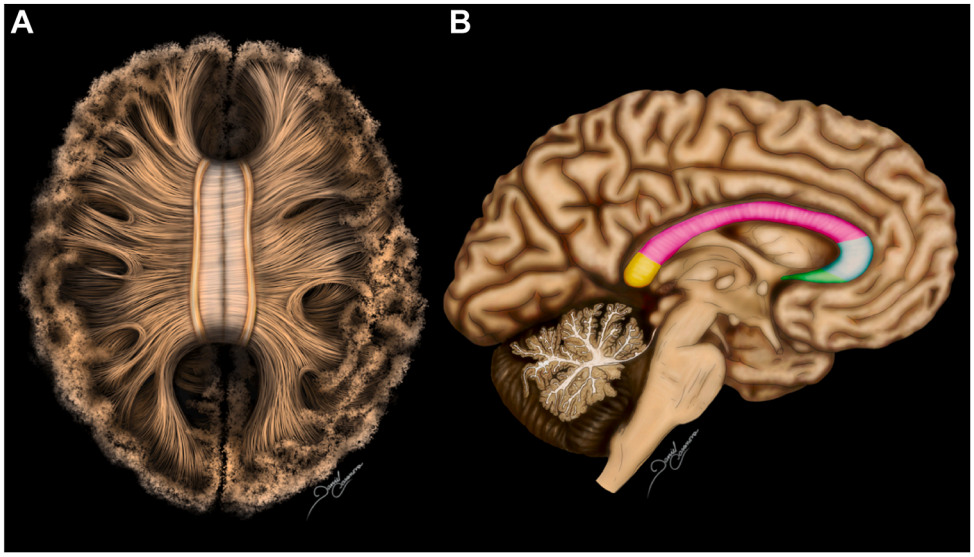

Figure 1. Representation of the standard anatomy of the typical corpus callosum. (**A**) Top view in cross-section of the corpus callosum. (**B**) Midsagittal colored view of the corpus callosum (in green the rostrum, in calypso the genu, in fuchsia the body, and yellow the splenium or tail).

applied a filtration process focusing on the titles and abstracts of these articles. From the initial selection, 46 articles were included; ultimately, 24 studies were chosen for meta-analysis. These studies were selected due to their thorough examination of the sample, detailed statistical data for each variant, and transparent methodology (Figure 3).

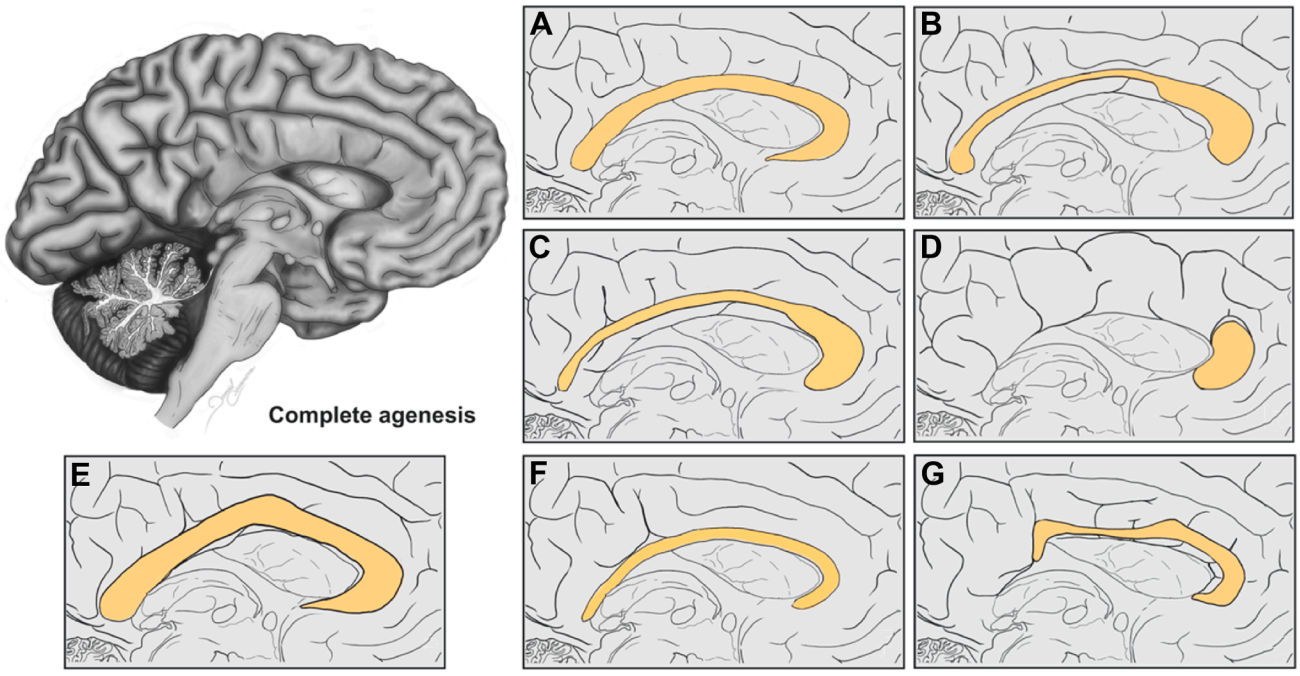

Figure 2. Description of the included variants of the corpus callosum agenesis (CCA). Kindly describe what depicts each variant. (**A**) Normal CC. Hypoplasia class of CCA: (**B**) hypoplasia without dysplasia CCA, (**C**) apple core CCA, (**D**) Anterior remnant CCA (*black arrow*). Hypoplasia with dysplasia class of CCA: (**E**) stripe CCA, (**F**) kinked CCA. (**G**) Complete agenesis. (**H**) Example of Probst bundles. Number of patients with each class of CCA and each subtype of CCA. CC, corpus callosum.

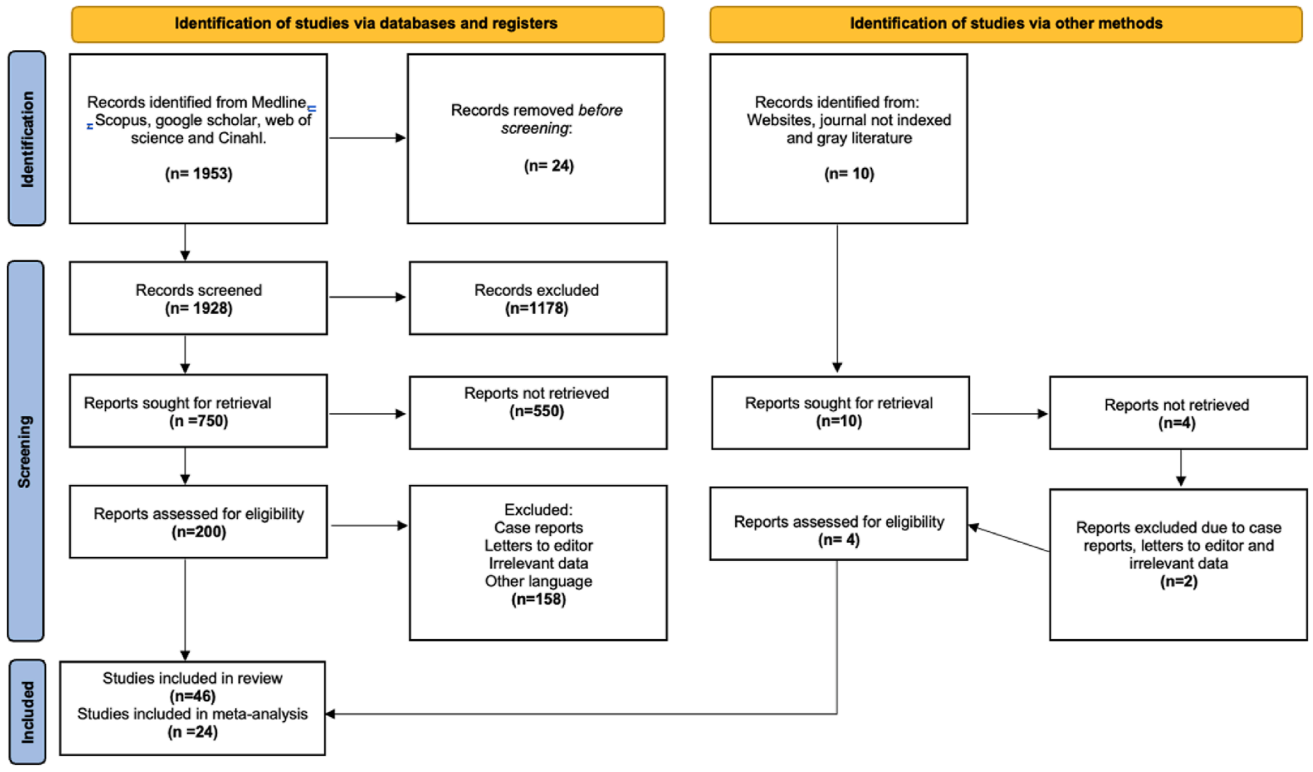

Figure 3. PRISMA statement-based search diagram. PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Characteristics of Included Studies

Number of included studies, the total number of subjects: 46 studies[1,20,26-68], 5,776,179 total individuals. Number of prevalence studies in the meta-analysis: 24 studies. Geographic region, Asia: 3 studies included.[29,45,68] Eight studies from Europe[1,27,28,34,37,38,58,62]: 12 studies from America.[20,30,32,39,40,44,46,50,52,63-65,67] One study was from Oceania[55], and no studies were from the African continent. About the gender of the individuals included in the studies, for the nonreported gender, there was a total subject of 5,118,037. While the studies that did report male and female subjects were 22 studies, 270 were females, and 250 were males, it is essential to mention that the reported studies only mentioned those with CC morphological variants. Related to the mean age, it was not reported since most of these studies were of neonates, and studies of adult patients were also added, so the mean age would not be fully representative of the sample studied (Table 1).

Prevalence of the Corpus Callosum Morphological Variants and Subgroups Analysis. Four proportion forest plots were created to calculate the prevalence of the CC morphological variants in the studies included in the present systematic review. Twenty-four studies[1,20,27-30,32,34,37-40,44-46,50,52,55,58,62-65,67,68] were included for the calculation of the prevalence of the CC morphological variants, presenting a prevalence of 18% (CI: 10%–25%). The heterogeneity of the samples included was 96.8%, which is high, and the sample was quite heterogeneous between the groups analyzed (Figure 4 and Table 2). The DOI plot showed symmetry. The LFK index was 0.344, suggesting low publication bias (Figure 5).

The first subgroup was cadavers, imaging, and fetuses. Among the imaging studies, 15 were included[1,20,27,30,31,38,39,45,46,50,63,64,68-70] (Figure 6), with a prevalence of 30% (CI: 11%–41%) and heterogeneity of 99.91%. The DOI plot showed symmetry. The LFK index was 0.69, suggesting low publication bias (Figure 7). To be more specific in the type of imaging, we have divided it into MRI, where we have included 7 studies[20,31,32,39,40,46,58] showing a prevalence of 3% (CI: 0.01%–5%) and a heterogeneity of 98.8% (Figure 8). For US images, we have included 6 studies[30,36,44,45,49,68] with a prevalence of 18% (CI: 0.3%–32%) and a heterogeneity of 93.2% (Figure 9). Among the fetus's subgroup, 8 studies[27,29,41,62,64-66,68], with a prevalence of CC morphological variants of 63% (CI: 28%–98%) and a heterogeneity of 99.12% (Figure 10). The DOI plot showed symmetry. The LFK index was −0.53, suggesting low publication bias (Figure 11). For the cadaver subgroup, 3 studies have been included[38,45,63] with a prevalence of 51% (CI: 0.1%–99.1%) and a heterogeneity of 99.11% (Figure 12). The DOI plot showed symmetry. The LFK index was 0.04, suggesting low publication bias (Figure 13). In this subgroup analysis, a significant difference was found in the

Table 1. Characteristics of the Studies Included in this Study Review by Year of Publication

Author(s)	Year	Region	Sample, N	Age/Sex	Prevalence	Symptoms	Circumstances	Variant Characteristics (Number)	Clinical Implications
Douglas et al.	1977	USA	-	—/—	—/—	No present	Comparison of normal and pathological anatomy in CT.	-	-
Ozaki et al.	1979	Japan	Mice	—/Adult mice	—/—	No present	The ipsilateral cortico-cortical projections were studied using horseradish peroxidase injections in the neocortex.	All with CCA	The intrahemispheric connections in the neocortex with CCA resemble those in typical mouse populations.
Jeret et al.	1985	EU	1447	—/—	33/1447	No present	A demographic compilation of the frequency of agenesis during the years 1978—1979 using CT.	CCCA (33)	It is documented that the inexperience of physicians with CT equipment may have contributed to an increase in the prevalence of agenesis due to possible misdiagnosis.
Bodensteiner et al.	1994	EU	445	Children under 17 years of age	14/445	No present	The MRI scans reviewed were conducted on children aged less than 17 years who underwent neuroimaging as part of a medical evaluation.	CCCA (5) CCPA (2) CCH (7)	Cerebral palsy has been associated with a thin CC in some reports. Cerebral palsy is a nonprogressive motor deficit resulting from injury to the brain at or around the time of birth.
Kimonis et al.	2004	EU	82	Different people of different ages	4/42 It is not 82 people, as only 42 had MRI and CT studies.	In this study, the raised intracranial pressure was the only symptom.	The NBCCS, fully delineated by Gorlin and Goltz, is an autosomal dominant disorder. Its main features include multiple basal cell carcinomas (BCCs).	Dysgenesis or agenesis of the CC (4)	The identification of a pathogenic mutation confirms a clinical diagnosis of NBCCS syndrome; however, not all patients presenting with clinical features of NBCCS will have detectable PTCH1 mutations.
László Sztriha	2005	United Arab Emirates.	16 children	(7 M and 9 F) Patients less than 12 years of age	16/16	Patients with Aicardi syndrome, L1 disease, and Mowat-Wilson syndrome	CCCA CCPA (hypogenesis: rostrum, posterior body) CCPA (hypogenesis: small splenium)	Upward displacement of the third ventricle, unrotated cingulate gyri, and absence of the cingulate sulcus, with sulci radiating toward the third ventricle.	Epilepsy, macrocephaly, developmental delays, spinal lipomas, intellectual disabilities, small optic discs, and abnormal eye movements.
Bedeschi et al.	2005	Italy	1753 patients	Average of 2.7 years/ 39 M and 24 F	63/1753	Cerebellar malformations, cardiac abnormalities, and skeletal abnormalities	Patients with CCA who received in-depth genetic, clinical, and laboratory testing	CCCA (30) CCPA (33)	CCA does not have a single prognosis, with outcomes varying from normal to severe psychomotor delays.

Fratelli et al.	2007	UK	117	Pregnant woman with 21—23 weeks of gestation	35/117	No present	This is a retrospective study of all cases of CCCA diagnosed prenatally.	Isolated CCA (35)	In prenatally diagnosed CCA, approximately one third of cases are isolated, whereas two thirds involve structural or chromosomal abnormalities.
Glass et al.	2008	EE.UU	3,440,576	—/—	630/3,440,576	No present	Characterize the prevalence, demographic risk factors, and malformations associated with CCA and CCH diagnosed during infancy.	CCCA (472) CCH (158)	Advanced maternal age was a significant risk factor for CCA, especially for infants with an identified chromosomal abnormality, where women aged 40 years and more.
Szabo et al.	2011	Hungary	185,486 live births	26 B and 12 G	38/185,486	Four patients exhibited developmental delays and intellectual disabilities, 3 patients presented with abnormal neurologic findings, and 2 were diagnosed with epilepsy.	CCCA or CCPA in 19 patients (13 B, 6 G) CCH in 19 patients (13 B, 6 G)	CC anomaly was associated with microcephaly, optic nerve hypoplasia, cerebellar vermis hypoplasia, or a wide cavum septum pellucidum.	CC anomalies were associated with encephalocele, hemimegalencephaly, polymicrogyria, cortical dysplasia, or wide cavum septum pellucidum, as well as non-CNS abnormalities such as dysmorphic features, congenital heart disease, limb anomalies, and hip dysplasia.
Owen et al.	2013	USA	18 individuals	—/10 M and 8 F	7/18	No present	CCA is linked to a genetic disorder affecting axonal orientation. The structural connectome of individuals with CCA is compared to that of normal humans.	CCA (7) Normal (11)	The CCA connectome exhibits greater interindividual variation than that of normal individuals, with extensive alterations in cortical and subcortical connectivity that extend beyond the absence of callosal fibers.
Erickson et al.	2014	USA	26 subjects	12 F:12 M	24/26	No present	The CCA group was as effective as the HC group in retaining and retrieving previously learned information.	Individuals with CCA were deficient in 2 domains of learning and memory on the CVLT-II: original learning and delayed recall.	The CCA significantly impairs learning and memory during recall. This impairment arises from insufficient coding in the anterior cingulate cortex rather than from issues related to attention or retention.

CT, computed tomography; CCA, corpus callosum agenesis; CCCA, corpus callosum complete agenesis; MRI, magnetic resonance imaging; CCPA, corpus callosum partial agenesis; CCH, corpus callosum hypoplasia; CC, corpus callosum; M, males; F, females; B, boys; G, girls; CNS, central nervous system; HC, healthy control; CVLT-II, Californian Verbal Test II; ASD, autism spectrum disorder; FTD, frontotemporal dementia; AD, Alzheimer dementia; GERD, gastroesophageal reflux disease; US, ultrasound; TDC, typically developing controls; HB, hepatoblastoma; WES, whole-exome sequencing; CNV-seq, copy number variation sequencing; NBCCS, nevoid basal cell carcinoma syndrome; PTCH1, protein patched homolog 1; EE.UU, United States of America; PIQ, perfomance IQ; CFA, caudal forelimb area; GTG, glutaraldehyde gelatyn.

Continues

Table 1. Continued

Author(s)	Year	Region	Sample, N	Age/Sex	Prevalence	Symptoms	Circumstances	Variant Characteristics (Number)	Clinical Implications
Ilik et al.	2014	Turkey	11-year-old G	11-year-old/F	1/1	Seizures, CCA, and colpocephaly	CCA was concomitant with colpocephaly.	Corpus callosotomy is performed in patients with generalized seizures.	Electrophysiologic and clinical findings indicate that other interhemispheric junctions may explain the ineffectiveness of corpus callosotomy.
Wiechec et al.	2014	USA	30 cases 21 subjects confirmed postnatally 9 subjects in the autopsy	The mean gestational age was 20.7 weeks (range: 19—23 weeks)	30/30	Seizures, severe neurodevelopmental delay, mild neurodevelopmental delay, and severe neurodevelopmental delay	Fetuses presenting with an absence of the cavum septi pellucidi, ventriculomegaly, and interhemispheric cysts.	29 cases were isolated CCCA, and one was complex CCCA together with vermian hypoplasia because of toxoplasmosis infection.	A stepwise ultrasound approach is recommended for diagnosing CCCA in the mid-trimester, as findings are less evident at this stage. Early diagnosis enables parents to make informed decisions regarding the continuation of the pregnancy.
Paul et al.	2014	USA	54 26 with CCA 28 with ASD	—/—	54/54	Autism symptoms	-	-	No present
Todorova Kitov et al.	2014	USA	20 fetuses/ 2238 au-autopsies	8 M and 12 F	20/20	Hydrocephalus, cerebellar hypoplasia, agenesis of the vermis cerebelli, polymicrogyria, lissencephaly, and clinodactyly.	CCCA, CCPA	CCA occurred during the 18th and 29th gestational weeks.	Prenatal diagnosis of CCA is challenging due to its small size and central location. It is generally possible after the 18th week of gestation, but becomes more reliable after the 23rd week when the CC is fully developed.
Neal et al.	2015	EE.UU	201	45 months/-	41/201	No present	Visualization of the morphology and variants of hypoplasia or agenesis of the corpus callosum using MRI	CCH without dysplasia (61) Apple core (36) Anterior remnant (6) Rudimentary body (3) Striped (30) Kinked (21) CCCA (41) Dysplasia (3)	These results further support the existence of significant heterogeneity in the spectrum of corpus callosum morphologies and associated brain malformations in individuals with CCA.
Calabro et al.	2015	Italy	1 patient	73-year-old F	1/1	No present	CCA is associated with FTD	Asymptomatic CCA (1)	The scientific relationship between AD and CCA is well supported. However, this case evaluates a potential link between CCA and FTD, suggesting that further research is necessary.

Beaulé et al.	2015	Canada	16 patients	9 M, 7 F/ 35.7 years	5/16	No present	This study compared the cortical thickness of adults with CCCA to that of HCs.	(5) CCA	Individuals with CCA exhibit consistent cortical abnormalities in motor, somatosensory, and visual areas, which differ from those of control patients due to patterns of plasticity.
Kidron et al.	2016	Israel	1290 autopsy of fetuses	—/—	50/1290	No present	External dimorphism and characteristics of Know syndrome	CCPA CCH Mixture between CCA and CCH	Linked to changes in fetal development that may disrupt growth or cause malformations.
Ingram et al.	2016	USA	86 parents of children with CCA	5—18 years	66/86	Difficulty with getting to sleep, night-time awakenings, and enuresis	Children with CCA may have accompanying health and psychosocial issues.	Children with CCA show significantly higher rates of sleep issues compared to their typically developing peers. This underscores the need for specialized support and interventions to tackle these sleep difficulties.	Infants and children with GERD often have trouble sleeping, while adolescents using proton pump inhibitors tend to sleep better. Additionally, GERD can contribute to obstructive sleep apnea.
Radhouane et al.	2016	Turkey	1 fetus	—/—	1/1	No present	Various chromosomal defects, including trisomies 18, 13, and 8, have been co-reported with CCA.	Genetic factors, alcohol toxicity, endogenous toxins causing lactic acidosis, vascular and metabolic defects, and congenital infections are closely linked to the etiology of CCA.	CCA is diagnosed through neuroimaging, using cranial ultrasonography during infancy and MRI in later years. MRI is more effective for diagnosing partial agenesis, while ultrasonography serves as a straightforward alternative for CCCA.
Paul et al.	2016	USA	30 adolescents and adults with CCCA and 30 HC	—/—	30/60	No present	Participants included 21 individuals with CCCA and 9 with CCPA	Undetected microscopic abnormalities may contribute to abnormal learning and memory. Postmortem analysis of 2 brains with CC dysgenesis showed significant differences in Von Economo neurons.	CCA impairs auditory and visual learning and memory, particularly affecting paired associates and delayed face memory. The results suggest multiple interpretations of how interhemispheric interactions via the CC contribute to memory.

CT, computed tomography; CCA, corpus callosum agenesis; CCCA, corpus callosum complete agenesis; MRI, magnetic resonance imaging; CCPA, corpus callosum partial agenesis; CCH, corpus callosum hypoplasia; CC, corpus callosum; M, males; F, females; B, boys; G, girls; CNS, central nervous system; HC, healthy control; CVLT-II, Californian Verbal Test II; ASD, autism spectrum disorder; FTD, frontotemporal dementia; AD, Alzheimer dementia; GERD, gastroesophageal reflux disease; US, ultrasound; TDC, typically developing controls; HB, hepatoblastoma; WES, whole-exome sequencing; CNV-seq, copy number variation sequencing; NBCCS, nevoid basal cell carcinoma syndrome; PTCH1, protein patched homolog 1; EE.UU, United States of America; PIQ, perfomance IQ; CFA, caudal forelimb area; GTG, glutaraldehyde gelatyn.

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Table 1. Continued

Author(s)	Year	Region	Sample, N	Age/Sex	Prevalence	Symptoms	Circumstances	Variant Characteristics (Number)	Clinical Implications
Govil-Dalela et al.	2017	USA	31 children	11 M, 20 F	4/31	No present	Children who did not have surgery still experienced seizures at the last follow-up.	Median age at seizure onset was lower in the Aicardi syndrome group compared to the nonsyndrome group.	Children with Aicardi syndrome experience earlier seizures, have poorer developmental outcomes, and display more prominent and extensive brain abnormalities on neuroimaging compared to those without the syndrome.
Anderson et al.	2017	USA	20 adults	9 M, 7 F	16/20	No present	The study investigates the emotional functioning of individuals with CCA	MRI showed the anterior commissure in all 15 cases and the posterior commissure in 14.	The capacity to experience and perceive basic emotions is relatively normal in adults with CCA.
Wegiel et al.	2017	USA	11 subjects with idiopathic autism 11 control subjects Total 22	Subjects with idiopathic autism (4—60 years old/8 M, F)	11/22	No present	CC anomalies related to idiopathic autism and axon count	CCH (8) CCPA (3)	CCPA and CCH relate to the reduction of axonal connections between cortical areas, which is associated with behavioral alterations observed in people with autism.
des Portes et al.	2017	France	50 cases	50 F	1:4000—1:5000	No present	Twelve pregnancies were terminated, one fetus died in utero, one outcome was unknown, and 36 babies were born, with 2 lost to follow-up. Thirty-four children were classified into 3 groups.	No present characteristic	Three patients with borderline intellectual functioning exhibited hypopituitarism and MRI anomalies. Long-term follow-up indicated low PIQ in younger children, which improved with age.
Jarre et al.	2017	Spain	78 fetuses	23 weeks/—	45/78	Cortical malformations, ventriculomegaly, posterior fossa, and midline anomalies	A 9-year MRI follow-up of 45 fetuses with corpus callosum issues correlated prenatal findings with postnatal MRI or necropsy outcomes.	(12) CCPA (33) CCCA	Fetal brain MRI is essential for diagnosing CCA and identifying associated anomalies, especially when CCA is suspected on US.

Ballardini et al.	2018	Italy	1,023,784 children born	—/—	255/1,023,784	Musculoskeletal malformations, particularly trisomy 18 and 13.	The Emilia Romagna study analyzed the prevalence and factors associated with CCA, classifying 255 subjects with CCA and CCH.	CCA (217) CCH (38)	CCA and CCH are complex conditions associated with frequent nervous system malformations. This study emphasizes that prenatal diagnosis is essential for making informed decisions regarding pregnancy continuation.
Siffredi et al.	2019	Australia	51 children	8—17 years/30 males and 21 females	21/51	No present	Altered microstructure of the anterior commissure in children with CCA	CCCA CCPA TDC	CCCA and CCPA are linked to changes in the anterior commissure. In CCPA.
Stoll et al.	2019	France	387,067 fetuses	(56 males, 43 females).	99/387,067 Prevalence of 2.56 per 10,000 73 (73.7%)	No present	Ventricular septal defect, renal agenesis, limb reduction defect, cleft lip, hydrocephaly, and hypospadias.	CCCA (79) CCPA (8) CCH (12)	In 73.7% of cases, CCA was associated with anomalies: 16.2% had chromosomal abnormalities, 13.2% had nonchromosomal dysmorphic conditions, and 44.4% had nonsyndromic multiple congenital anomalies.
Luckie et al.	2020	USA	2 babies (patients)	31 and 36 weeks of gestation/F	2/2	Microcephaly, premature babies.	Multiple congenital anomalies, including HB.	2 patients with Aicardi syndrome and HB.	CCA is associated with HB; HB is related to gestational risks, multiple congenital anomalies, and low birth weight.
Bayram et al.	2020	Turkey	75,843 fetuses	—/—	109/75,843	Ventricular septal defect, microcephaly, and cleft lip and/or palate	CNS malformation, isolated and complex CCA.	- Patients who successfully overcome their conditions. - Those facing mortality in the postnatal phase. - Choices between elective terminations and spontaneous abortions.	Isolated CCA is associated with a favorable outcome for the individual if they do not have congenital anomalies. On the other hand, the complex CCA.
Raile et al.	2020	Germany	23 patients	Average of 3.8 years/ 11 F, 12 M	23/23	CNS malformations, such as gray matter heterotopias, polymicrogyria, or pachygyria	It involves fetal detection and postnatal follow-up with neuro-evaluation, developmental assessment, and genetic testing.	Isolated CC malformation (15). Associated cerebral malformations (4). Malformations plus intracranial cyst (4).	More than half of prenatally diagnosed CCA patients show favorable development, but predicting future complications is challenging due to variability in outcomes, making prenatal counseling difficult.

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Table 1. Continued

Author(s)	Year	Region	Sample, N	Age/Sex	Prevalence	Symptoms	Circumstances	Variant Characteristics (Number)	Clinical Implications
Vivekanandan et al.	2020	Canada	1 patient M	15-week gestation US	1/1	Progressive headaches, his gross and fine motor milestones were delayed (11 to 12 months 29 stage), but the remainder of his neurological examination was normal.	Interhemispheric cyst and CCA	Interhemispheric cysts with agenesis of the corpus callosum (CC) and cortical abnormalities consistent with pachygyria or polymicrogyria, diagnosed at a young age.	This is the first reported case of an interhemispheric cyst with CCA exhibiting choroidal and ependymal features. It highlights the importance of ongoing surveillance due to the potential for expansion or symptomatic progression, which may necessitate surgery.
Bartha et al.	2021	Austria	6 children	6—15 years/—	6/6	No present	CCCA is associated with impaired functions in specific language domains and reduced right intrahemispheric activity.	CCCA (3) CCPA (3)	CCCA is associated with poor verbal fluency and decreased right intrahemispheric and interhemispheric connectivity. Therefore, connectivity correlates with improved language management.
Labon et al.	2021	Switzerland	2 babies	A girl and a fetus	2/2	Axial hypotonia and mild dysmorphic features include a saddle nose, low-set ears, poor eye contact, and pronounced hypotonia.	CCA, hypoplastic anterior commissure, and absent interthalamic adhesion	Observed novel compound heterozygous KDM5B variants associated with impaired brain development, craniofacial dysmorphism, and CCA.	In case 1, the pregnancy was uneventful; however, dysmorphic features later developed, including a large forehead, a prominent metopic region, and other facial and physical abnormalities. Case 2, a sibling from a subsequent pregnancy, was diagnosed with partial CCA during the second trimester through ultrasound, which fetal MRI confirmed.
Adem Yokus	2022	Turkey	1 F patient	11-month-old	1/1	Increase in head circumference	CCCA is a cystic lesion measuring 113 × 74 × 52 mm, located in the midline of the frontoparietal interhemispheric region.	CCCA and colpocephaly were present, but neurological development was normal, and there was no hydrocephalus.	CCA was present, but the posterior fossa and fourth ventricle appeared normal. Since neurological development was normal and there was no evidence of hydrocephalus, no intervention was required.

Wendy et al.	2022	USA	127 fetuses	—/—	45 isolated-complete, 17 isolated-partial, 46 complex-complete, and 19 complex-partial CCA. Of 75 live births, 72 had postnatal evaluations.	Problems with fine and gross motor function, language development, ophthalmologic and endocrine abnormalities, seizures, genetic syndromes, and impaired cognition.	CCCA CCPA	Mild ventriculomegaly and colpocephaly are often linked to CCA; if these are the sole findings, the condition is categorized as isolated CCA.	Cases of complex CCA showed lower live birth rates and higher rates of elective termination and intrauterine demise compared to isolated CCA cases. The 3 fetuses with intrauterine demise were identified as having complex CCPA.
Vola et al.	2023	Italy	-	—/36 male and 8 female	-	No present	Morphological analysis of such fetuses using fetal MRI to determine if there are indicators that could be used to delineate a genetic substrate of the phenotype to inform future studies.	-	This characteristic and repetitive location of the CFA does not favor the hypothesis of a clastic etiology, which is typically associated with more randomly located anomalies; instead, it supports the genetic etiology hypothesis.
Zheng et al.	2023	China	10 fetuses	Average of 27 weeks/4 females and 6 males	6/10	Symptoms range from none to severe neurodevelopmental issues, such as epilepsy, learning disabilities, and psychiatric disorders. Syndromic agenesis of the corpus callosum presents more severe symptoms than isolated cases.	Chromosomal analysis on cultured amniotic fluid cell samples after informed consent, using GTG-banding according to standard procedures.	CCCA (6)	CCCA is a common congenital brain malformation that may occur alone or as part of a syndrome. It is linked to reduced interhemispheric and right language network connectivity, correlating with decreased verbal abilities.
Su et al.	2023	USA	25 individuals	—/—	25/25	No present	Individuals with CCA exhibit limited semantic imagination and verbal problem-solving abilities; however, they improve with additional trials and adequate cues, much like their control counterparts.	CCPA (6) CCCA (18)	Individuals with CCA typically struggle with more abstract tasks but perform more normally with functions that are highly practiced or less complex.

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Table 1. Continued

Author(s)	Year	Region	Sample, N	Age/Sex	Prevalence	Symptoms	Circumstances	Variant Characteristics (Number)	Clinical Implications
Ecker et al.	2023	Belgium	148 fetuses	24.3—24.7 weeks	62 CCCA 83 CCPA	No present	Including all singleton fetuses diagnosed in utero with abnormal development of the CC from January 2007 to December 2017.	In 51 of 86 cases, either the splenium (47.7%) or the corpus and splenium (11.6%) were missing. The rostrum was the missing part in 7 cases (8.1%), either in isolation or combined with the genu, or combined with both the genu and the corpus.	CCPA requires neurosonography, fetal MRI, and genetic tests to differentiate between isolated and nonisolated cases. After the prenatal diagnosis of isolated CCPA, 60% have favorable outcomes; however, school-age disabilities such as speech, behavior, and motor deficits may emerge.
Wei et al.	2024	China	68 fetuses with CCA	—/—	8/68	No present	The medical records of pregnant women diagnosed with CCA in the second or third trimester by ultrasound and MRI were prospectively collected based on the work-up flow at Shanghai First Maternity and Infant Hospital between January 2016 and November 2022.	Cases with pathogenic copy number variants (8)	The neurological outcome of the children who were followed up postnatally, most of whom had isolated CCA, showed normal neurodevelopment in 91.7% of cases.
Sun et al.	2024	China	40 individuals	24 weeks of average gestation/ 20 males and 20 females	40/40	Cerebellar dysplasia and hydrocephalus were the most common abnormal developments.	Genetic and clinical results are analyzed in patients with nonisolated CCA and isolated CCA.	Nonisolated CCA (29) Isolated CCA (11)	Prenatal genetic analysis of fetuses with CCA is essential, as monogenic disorders are the primary cause. WES can enhance detection in cases with negative karyotype or CNV-seq results.
Maharajh et al.	2024	South Africa	30 embalmed brains	15 M, 15 F	—/—	No present	-	-	This study aimed to detail the anatomy of the CC isthmus in South African cadavers, measuring its size using Witelson's parameters.

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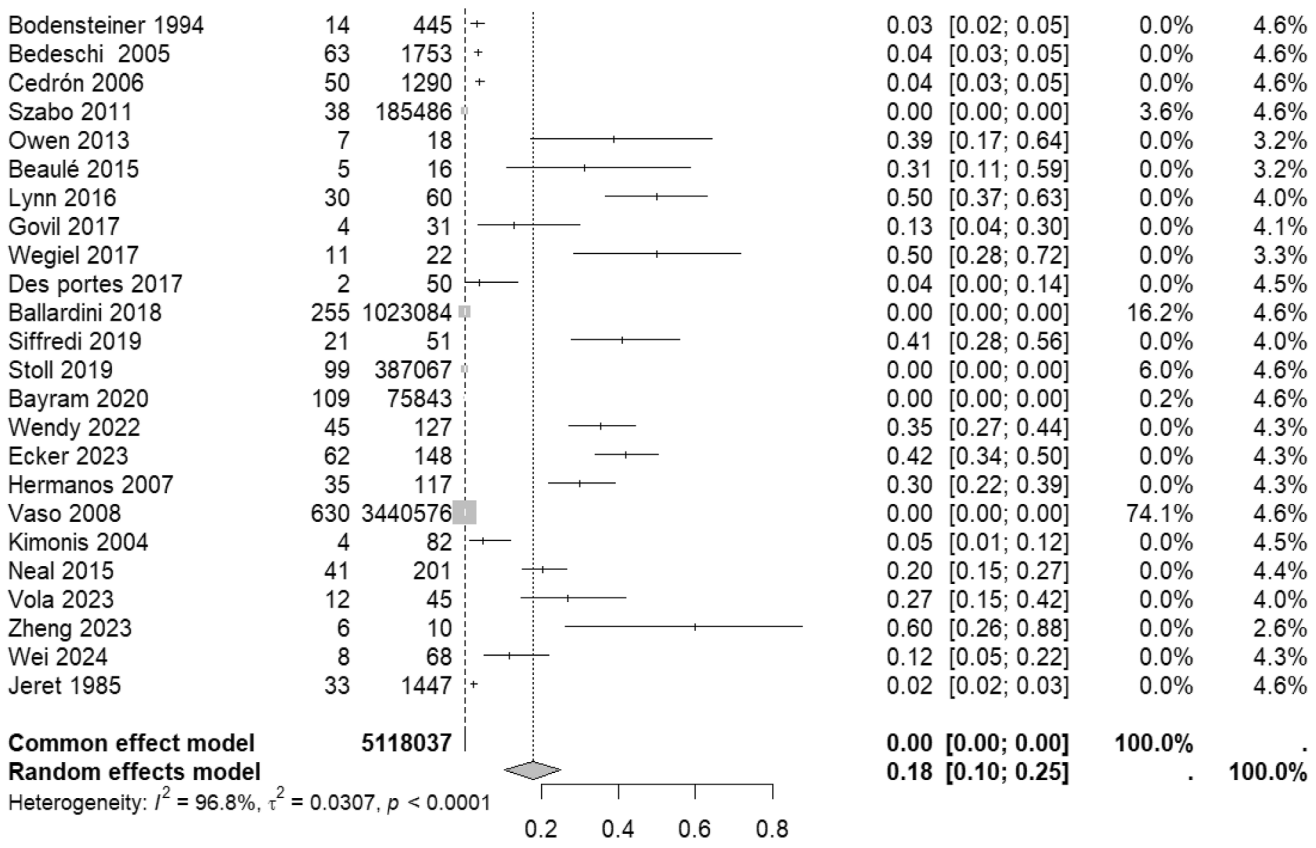

Figure 4. Forest plot of studies included in the prevalence meta-analysis.

presence of diagnostic images (P = 0.001). The second subgroup analysis was for the continents from which the included studies were conducted. Three studies from Asia were included[29,45,68], presenting a prevalence of 20.61% (CI: 18.11%–21.39%) and a heterogeneity of 72.12%. From Europe, 8 studies were included,[1,27,31,34,37,38,58,62] presenting a prevalence of 2.24% (CI: 1.01%–4.94%) and a heterogeneity of 89.46%. From America, 6 studies were included[30,32,39,40,44,46,50,52,63-65,68] presenting a prevalence of 0.92% (CI: 0.54%–1.99%) and a heterogeneity of 77.22%. From Oceania, one study was included[55], presenting a prevalence of 4.93%. Heterogeneity and CI cannot be estimated as only one study was included. Prevalence articles from Africa were not included, so these were not analyzed. For this subgroup analysis, there was a significant difference in the greater presence of studies in the Asian, American, and European continents (P = 0.001). Another subgroup analyzed was the type of morphological variant present in the CC. First, for CCPA, 11 studies were included[1,31,32,34,37,45,49,55,58,63,65], with a prevalence of 13% (CI: 3%–24%) and a heterogeneity of 97% (Figure 14). The DOI plot showed symmetry. The LFK index was 0.27, suggesting low publication bias (Figure 15). For the CCCA, 22 studies were included[1,20,28-30,32,37-40,44-46,50,52,55,58,62-65,67,68] with a prevalence of 51% (CI: 32%–69%) and a heterogeneity of 99.44% (Figure 16). The DOI plot showed symmetry. The LFK index was 0.58, suggesting low publication bias (Figure 17). For this subgroup analysis, a statistically significant difference existed (P = 0.0001). Finally, the subgroup analysis performed for the sex of the included subjects, 23 studies showed male with the variant[1,20,27-30,32,34,37-40,44-46,50,52,55,58,62-65,68] which presented a prevalence of 1.38% (CI: 1.01–1.91) and a heterogeneity of 81.22%. While 24 studies reported females with CC morphological variants[1,20,27-30,32,34,37-40,44-46,50,52,55,58,62-65,67,68], presenting a prevalence of 1.21% (CI: 1.01–1.61) and heterogeneity of 84.49%. For this subgroup analysis, there was no statistically significant difference in favor of the CC presence in males compared to that in females (P = 0.359) (Table 3).

Sensitivity Analysis. For the included studies, not only was there statistical heterogeneity but also there was heterogeneity due to the high number of subjects in some studies, or also due to a

Table 2. The Prevalence of Corpus Callosum Agenesis in the Included Studies is Equal to or Less Than 50%

Author	Year	Total Number of Cases (Sample)	Cases Identified
Bodensteiner et al.	1994	445	14
Bedeschi et al.	2005	1753	63
Kidron et al.	2006	1290	50
Szabo et al.	2011	185,486	38
Owen et al.	2013	18	7
Beaulé et al.	2015	16	5
Lynn et al.	2016	60	30
Govil et al.	2017	31	31
Wegiel et al.	2017	22	11
Des portes et al.	2017	50	34
Ballardini et al.	2018	1,023,084	255
Siffredi et al.	2019	51	21
Stoll et al.	2019	387,067	99
Bayram et al.	2020	75,843	109
Wendy et al.	2022	127	45
Keersmaecker et al.	2023	148	28
Fratelli et al.	2007	117	35
Glass et al.	2008	3,440,576	630
Kimonis et al.	2004	82	4
Neal et al.	2015	201	41
Vola et al.	2023	45	12
Zheng et al.	2023	10	5
Wei et al.	2024	68	68
Jeret et al.	1985	1447	33

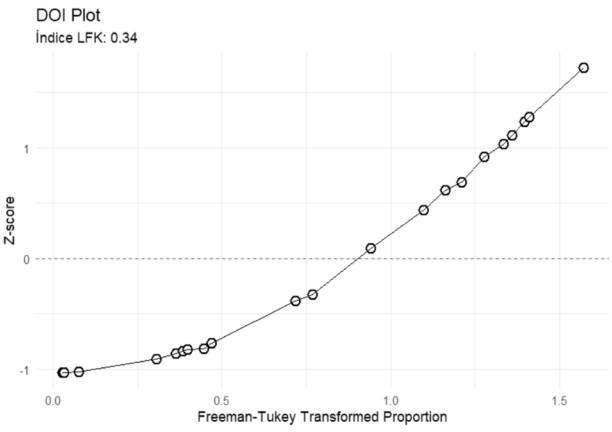

Figure 5. DOI plot and index LFK of the studies included in the prevalence meta-analysis. LFK, Luis Furuya-Kanamori.

smaller number of subjects and a high prevalence of variants of the CC; so to eliminate the overestimation of these data, we performed a sensitivity analysis for both factors mentioned above; first, for the sensitivity analysis with studies with prevalence less than 50%, the results were as follows: prevalence of 9% and a CI of 2% to 16%, with a heterogeneity of 95.9% (Figure 18), with respect to the data reported in the forest plot with all the studies included there was a decrease of 9% which indicates 50% of the original value, so the studies with a prevalence greater than 50% influence the original results in a statistically significant way ($P = 0.001$). For the other sensitivity analysis of results, studies with a

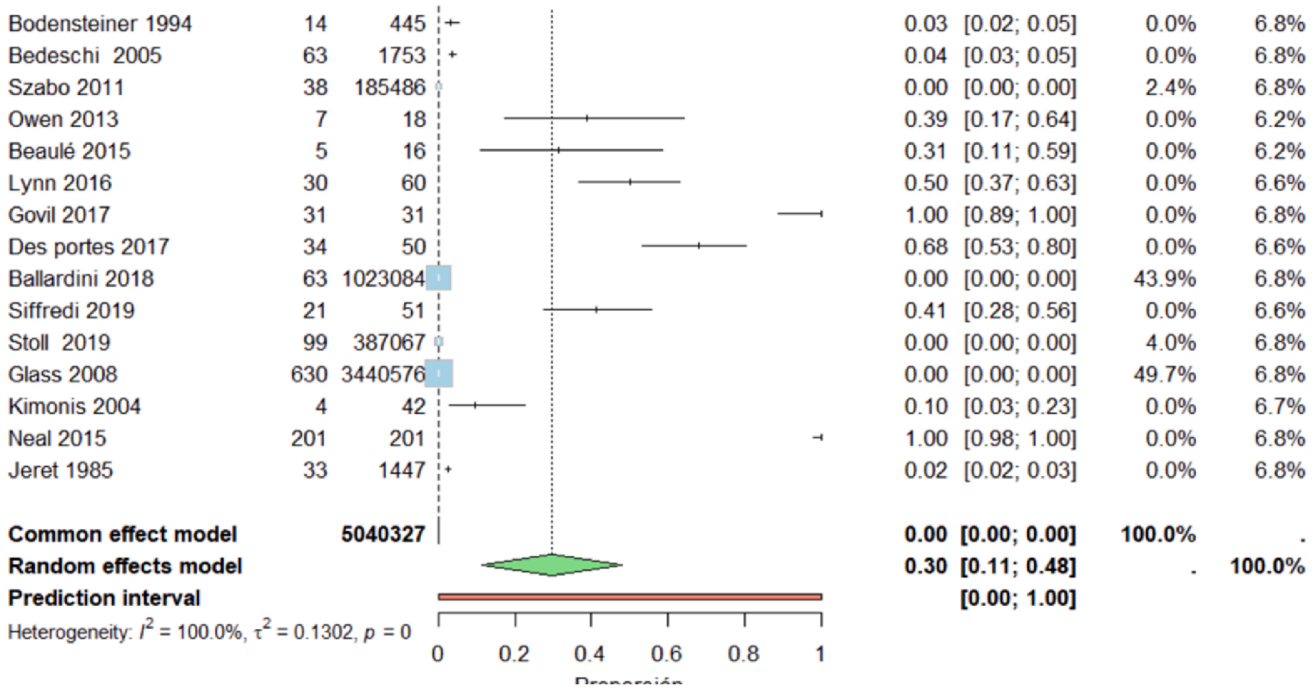

Figure 6. Forest plot imaging subgroup.

number greater than 10,000 subjects have been eliminated, reporting a prevalence of 51% with a CI of 32% to 69% and a heterogeneity of 95%. Given the results, we can also show that by eliminating studies with a population greater than 10,000, the increase more than doubles, which is why these studies influence a decrease in the overall prevalence since it is statistically significant (Figure 19).

Publication Bias Analysis. For the analysis of bias of results of this meta-analysis, we have performed a publication bias analysis using funnel plot; for this analysis, the most representative forest plots of this study have been analyzed; first, the funnel plot for the global analysis of the results showed that most of the studies were outside the range of the triangle, which represents a high asymmetry between the studies (Figure 20); on the other hand, Egger's test (P = 0.01) corroborated this observation, indicating that studies with negative results may not be published. It is recommended to take this bias into account when interpreting the results of the present study (Figure 19). For the forest plot of studies with a prevalence no greater than 50%, the funnel plot showed an evident asymmetry and only 4 studies were found within the established range; on the other hand (Figure 21), Egger's test (P = 0.033) corroborated this observation, indicating that studies with negative results may not be published. It is recommended to take this bias into account when interpreting the results of the present study (Figure 20). Finally, the forest excluding studies with a number

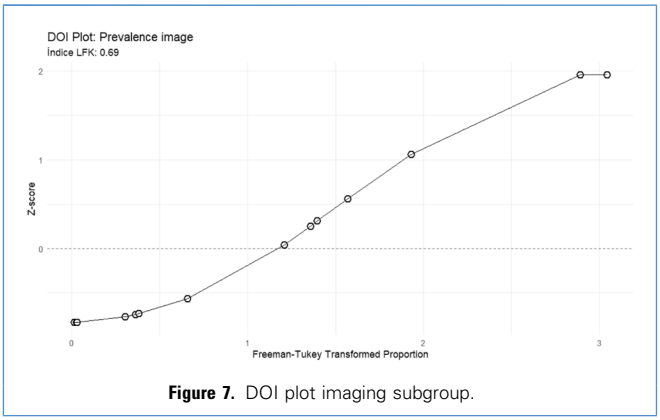

Figure 7. DOI plot imaging subgroup.

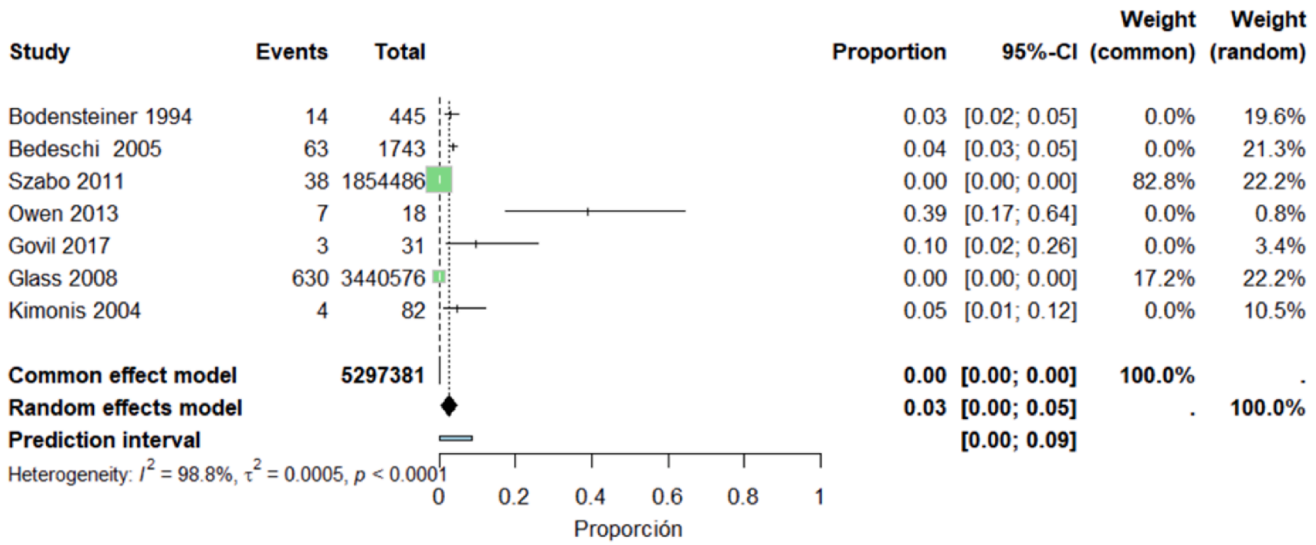

Figure 8. Forest plot of MRI. MRI, magnetic resonance imaging.

greater than 10,000 showed a funnel plot with a high asymmetry since only 3 studies were within the range; for the Egger test, a value (P = 0.015) corroborated this observation, indicating that studies with negative results may not be published. It is recommended to take this bias into account when interpreting the results of the present study (Figure 22). The data show that the results should be interpreted with caution.

Quality of Evidence Report with Grading of Recommendations, Assessment, Development and Evaluation. The quality of evidence on the presence of CCA in subjects assessed globally was classified as very low due to the differences in the sample sizes of the different studies and the varied prevalence they showed. This demonstrates that some studies may overestimate the results for the presence of CCA. The quality of evidence for CCA with a presence of less than 50% was classified as moderate, indicating that data with a prevalence of less than 50% are more representative and can be better interpreted in relation to the presence of CCA. For the quality of evidence for prevalence with a sample size of no more than 10,000, the quality of evidence was classified as low because some data underestimate the total proportion of studies included. Regarding the analysis of the quality of evidence for imaging, the

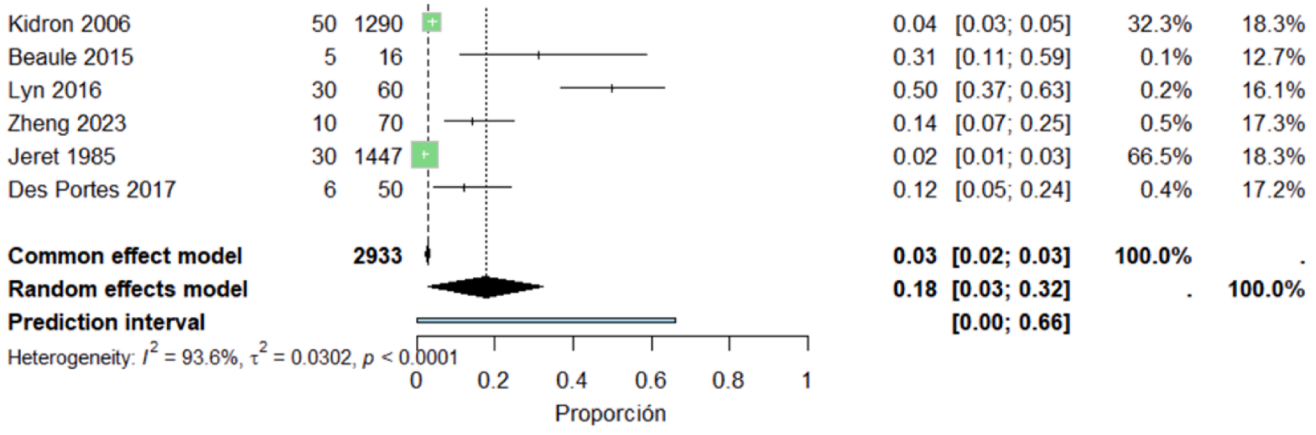

Figure 9. Forest plot of ultrasound.

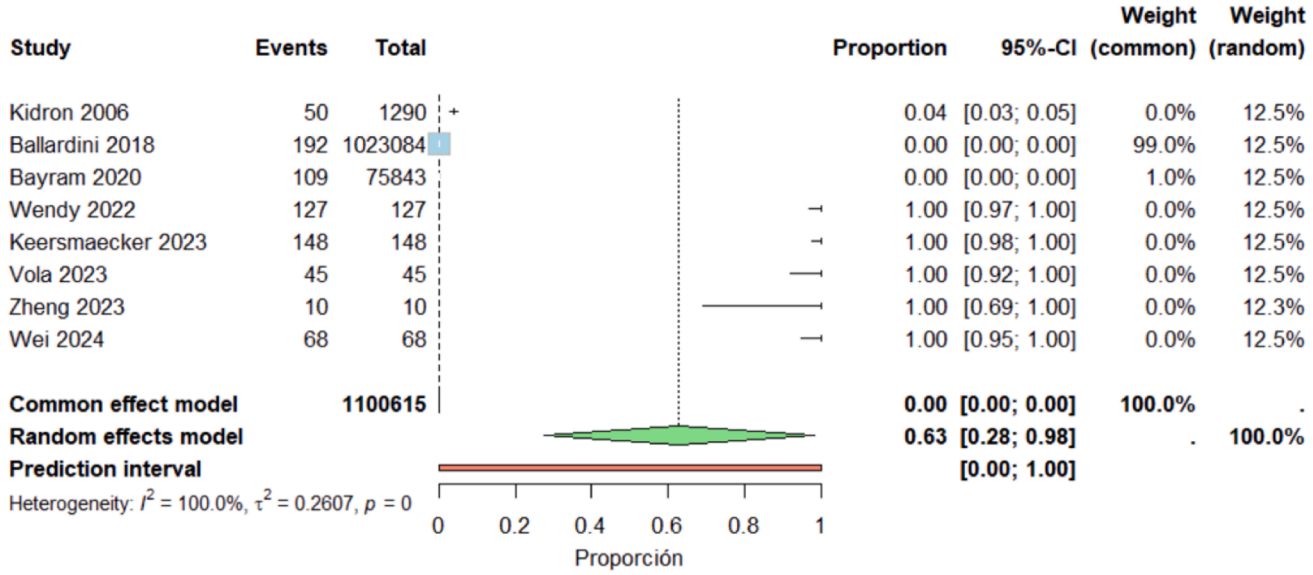

Figure 10. Forest plot of studied sample fetuses.

quality of evidence was classified as low since the proportion of studies that evaluated subjects with imaging varied greatly. For the specific analysis of the images, MRI showed a moderate quality of evidence, since when grouping the data by image type the analysis was more specific and the same diagnostic method could be better grouped for the presence of CCA. For the analysis of images through US, the level of quality of evidence was moderate since the grouping of the diagnostic method specifically by image was clearer for the sample with the presence of CCA. For the analysis of fetuses, the level of quality of evidence was moderate since the sample is representative, but there was still a minimal number of studies that could have overestimated the data and increased the heterogeneity. Regarding the analysis of the sample in cadavers, the level of quality of evidence for the subjects included in this sample was very low, since the sample was very low, and the prevalence is evidently overestimated since the proportion is inflated for this analysis. For the analysis of subjects with CCPA, the level of evidence quality was moderate, since the grouping allows for an orderly distinction between subjects with CCPA and CCCA. Finally, for the analysis of the quality of evidence for CCCA, the level of evidence quality was low because, although the sample was grouped by CCA characteristics, the sample and prevalence were highly diverse (**Supplementary Table 3**). For the grouped data, the level of evidence quality ranged from very low to moderate; therefore, the grouped data in the analyses should be interpreted with caution.

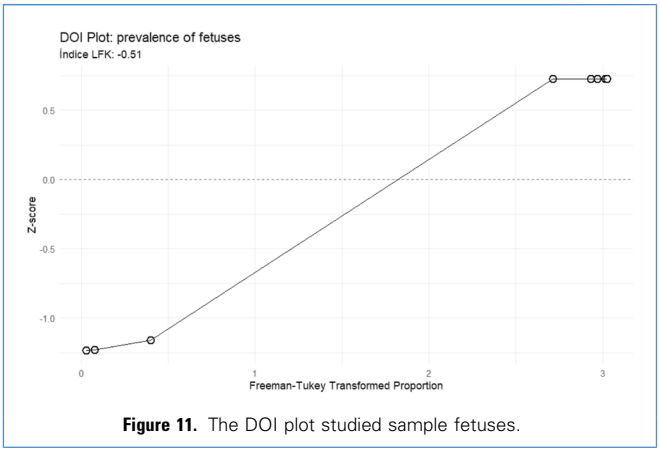

Figure 11. The DOI plot studied sample fetuses.

Risk of Bias of Included Articles. Thirty-seven studies met the criteria for evaluation using the AQUA checklist for anatomical studies, which analyzed bias across 5 domains. Of these 5 domains, 4 included studies[33,39,54,59] that presented a high risk of bias in the methodology and characterization domain, while 5 studies[56,58,61,63,64] exhibited a high risk of bias in the descriptive anatomy domain. Finally, in the reporting of results domain, 10 studies[1,20,30,32,34,37,52,55,58,62,68] were found to have a high risk of bias, indicating that results from at least 10 articles should be interpreted with caution (**Figure 23**).

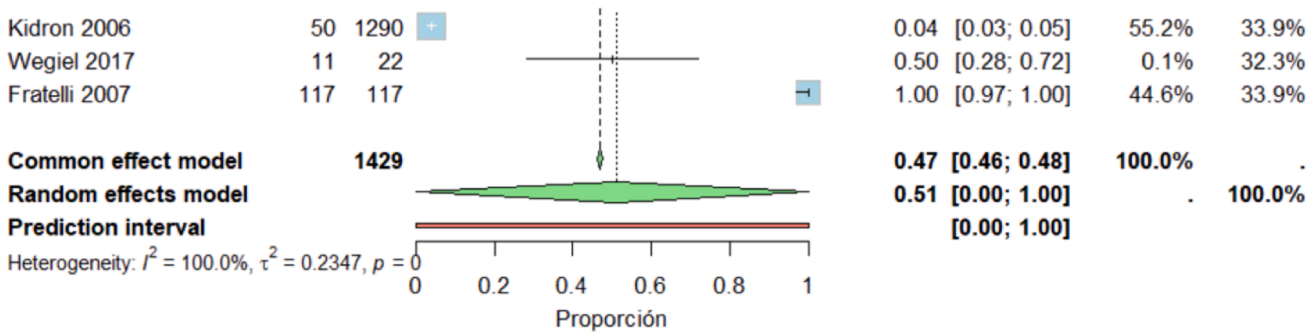

Figure 12. Forest plot cadavers.

DISCUSSION

This systematic review examines CC morphological variants through a meta-analysis. The most commonly studied variants are the CCA cases, which include CCPA and CCCA, as they are crucial for communicating with the cerebral hemispheres.[44] CCA can cause severe complications and functional impairments, making its study essential for effective clinical management of affected patients.

Previous Studies on Corpus Callosum Agenesis

Previous meta-analyses have focused on the morphological characteristics of CC variants. Sileo et al. (2020)[71] noted that some brain abnormalities detected via fetal MRI may not be visible on prenatal assessments, emphasizing the need for thorough parental counseling. This complexity can affect clinical management, as conditions like hydrocephalus may go undetected early on. Early recognition of anomalies is crucial, particularly for decisions regarding severe CCA. Our meta-analysis highlights the variability in CC morphology and the importance of accurate prenatal diagnosis. Fetal MRI, serving as a critical complement to US, often reveals complexities that US might miss, reinforcing the need for early intervention. Although neuropsychological deficits related to CC anomalies are well known, emerging evidence regarding cortical abnormalities and findings related to the posterior fossa adds further complexity to prognosis and management. In summary, the studies reviewed underscore the importance of comprehensive antenatal diagnosis, the limitations of US, and the enhanced role of fetal MRI in improving clinical outcomes for CCA. Mustafa et al.[72] highlighted the association of CCA with various neurological dysfunctions, such as epilepsy and structural brain abnormalities. They emphasized the need for a comprehensive, multidisciplinary evaluation of affected patients. This underscores the importance of neuroimaging techniques, like fetal MRI, for accurate prenatal diagnosis and effective postnatal care planning. Additionally, our research reveals considerable variability in the prognosis of individuals with CCA, which may depend on factors such as CC integrity, other brain abnormalities, and the impact on cognitive functions like learning and memory. In conclusion, the information provided in our study positively and critically complements the previous study's findings regarding early screening for CCA prenatal diagnosis. A thorough understanding of the clinical impact of this condition highlights the significance of accurate diagnostic tools like early screening, which facilitate early detection and appropriate care planning for these patients. Zhang's meta-analysis[73] emphasizes a key finding consistent with our research and the other study: enhancing diagnostic accuracy. While the US demonstrates high specificity, its moderate sensitivity means that there are still instances of false negatives. This limitation can delay the identification of CCA and ultimately impact clinical planning. To address these limitations, incorporating routine neurosonography

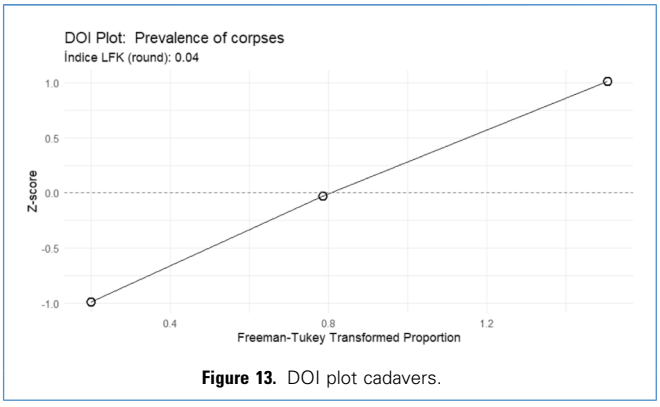

Figure 13. DOI plot cadavers.

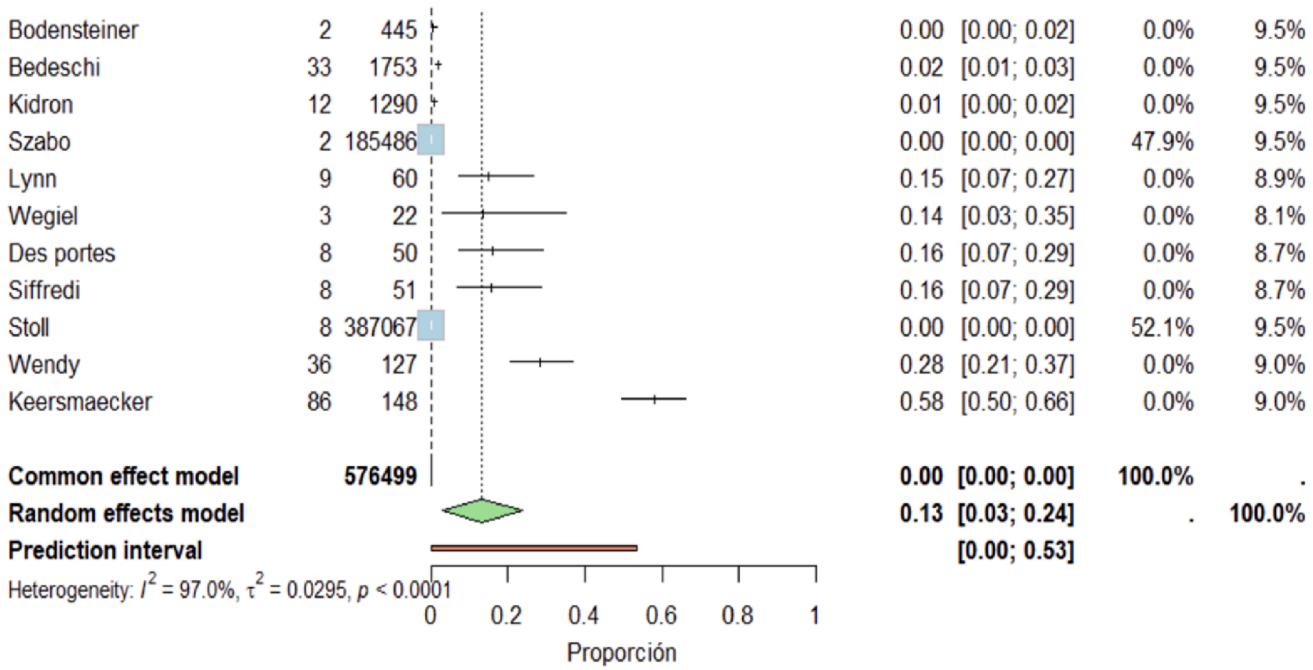

Figure 14. Forest plot subgroup CCPA. CCPA, corpus callosum partial agenesis.

and fetal MRI in cases where abnormalities are suspected could be beneficial. This combined approach would also aid in detecting additional malformations frequently associated with CCA.[71-73]

Global Clinical Considerations

Our research provides an overview of the clinical implications of CCA. We discuss the typical anatomy of the CC and how agenesis can often be diagnosed early, even in the fetal stage. Understanding the anatomy and embryonic development of CCA is essential for effective prenatal diagnosis through exome sequencing. Once identified, a multidisciplinary team is

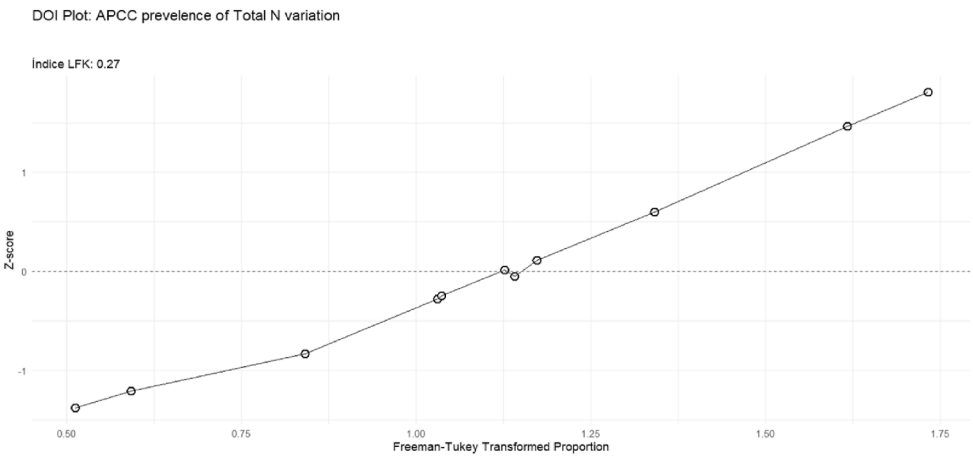

Figure 15. DOI plot subgroup CCPA. CCPA, corpus callosum partial agenesis.

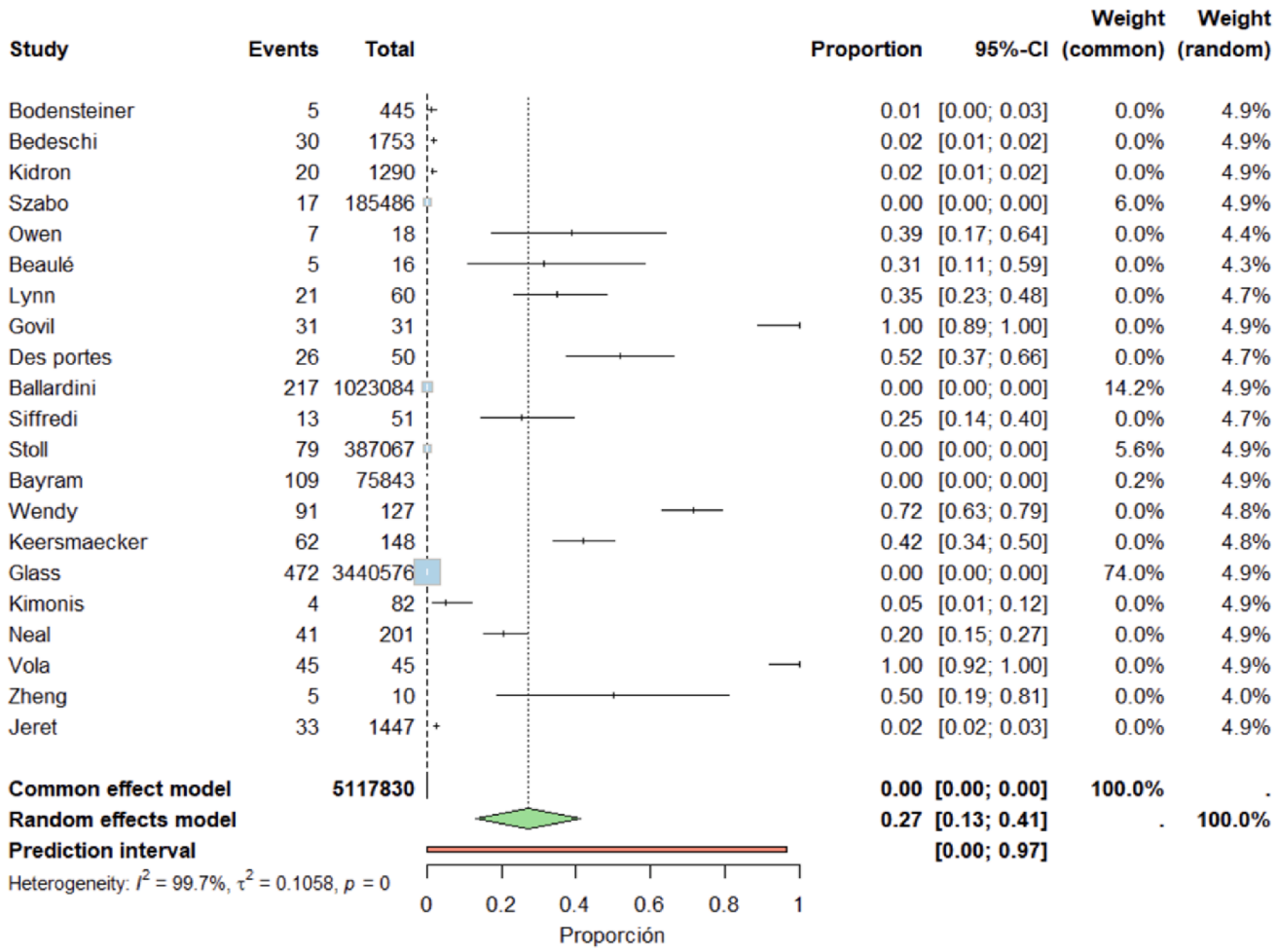

Figure 16. Forest plot subgroup CCCA. CCCA, corpus callosum complete agenesis.

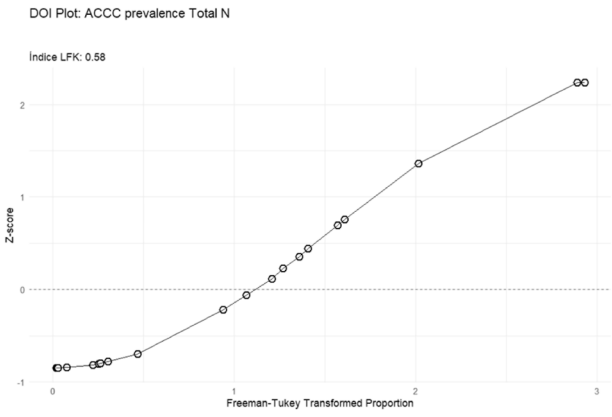

Figure 17. Forest plot subgroup CCCA. CCCA, corpus callosum complete agenesis.

vital for determining management strategies. Standard US often lacks sensitivity, making advanced technologies like neurosonography and MRI necessary for accurate diagnosis and understanding neurological implications. CCA poses significant challenges by altering brain structure and affecting interhemispheric connectivity. It typically presents findings such as Probst's bundle formation and ventriculomegaly, although interhemispheric connectivity may be less affected. CCA occurs in about 1 in 4000 births and represents 3%–5% of individuals undergoing neuroimaging due to neurodevelopmental disorders. The combined prevalence of CCA and CCH is estimated at 1.8 to 10 in 10,000 births, highlighting the

Table 3. Subgroup Analysis of the Studies Included in the Prevalence Meta-Analysis of Corpus Callosum Agenesis

Parameters	Number of Studies and Subjects	Prevalence of Variants	95% CI	I^2	*P* Value
Overall	24	0.1811	0.1056—0.2412	96.8%	-
By study type					
Cadavers	3 (1429)	0.51	0.01—0.99	99.11%	0.001
Imaging	15 (3,440,915)	0.30	0.11—0.48	99.91%	
Fetuses	8 (466,712)	0.63	0.28—0.98	99.12%	
By geographic area					
Asia	3 (77,143)	0.2061	0.1811—0.2139	72.12%	0.001
Africa	-	-	-	-	
Europe	8 (1,598,417)	0.0224	0.0101—0.0491	89.46%	
America	12 (3,405,274)	0.0092	0.0054—0.0199	77.22%	
Oceania	1 (519)	0.0493	-	-	
By agenesis type					
CCPA	11 (576,499)	0.13	0.0311—0.24	97%	0.0001
CCCA	22 (5,117,830)	0.27	0.13—0.41	99.42%	
By gender					
Male	23 (2,436,732)	0.0138	0.0101—0.0191	81.22%	0.359
Female	24 (2,643,022)	0.0121	0.0101—0.0161	84.49%	

CI, confidence interval; CCPA, corpus callosum partial agenesis; CCCA, corpus callosum complete agenesis.

importance of early detection and intervention. A meta-analysis of 37 studies revealed significant variability in findings, with more than 80% heterogeneity. Most studies focused on Asian populations, but our review found no ethnic differences among individuals with CCA. No associations were identified between CCA and maternal age, environmental factors, or geographic region,[74] nor was there a significant correlation with the subjects' sex. Determining the accurate age of diagnosis remains complex, as it can occur during fetal development or at birth.

The prenatal diagnosis or suspect of CCA using neuroimaging techniques is a challenge not only for the newborn child but also for the parents. It is important to educate them about the condition, detailing possible causes as well as its relationship to pathologies such as cognitive impairment, developmental delay, and epilepsy. It is also important to note that not all newborns with CCA will necessarily present with these secondary pathologies. If the diagnosis of CCA is confirmed, prenatal follow-up through fetal neuroimaging with detailed USs or fetal MRI is essential. This is done not only to identify and describe the agenesis itself but also to rule out other structural abnormalities in brain tissue. In addition to neuroimaging follow-up, it is important for a team of specialists such as pediatric neurologists, neurosurgeons, and geneticists to evaluate fetal development and the newborn's growth after birth. It is very common for a patient with CCA to experience epilepsy, which is why it is important for a team of specialists to evaluate the disease by observing seizures and monitoring with electroencephalograms to define a therapeutic plan with antiepileptic drugs, counseling and family support for living with an epileptic person, and knowing how to react during a seizure episode.

Anatomical and Statistical Characteristics

The typical anatomy of the CC consists of interhemispheric commissural fibers organized into 4 portions. In CCCA, imaging shows a total absence of the CC. In cases of CCPA, diagnosing the condition can be more complex due to the specific region affected. While the splenium is the most common site for CCPA, agenesis can also occur in other areas. A meta-analysis of 24 studies indicated a prevalence of CCA of 19%, although this figure may be overestimated due to selection biases in various studies. Some multicentric studies with large sample sizes reported a much lower prevalence, warranting cautious interpretation of the results. To investigate differences between study groups, we analyzed samples based on diagnostic techniques, geographical origin, specific variants of the CC, and participant sex. We found a statistically significant difference in prevalence by continent, with Asia reporting a statistically significant level of $P = 0.001$. The above should be taken with caution since there were geographic regions that did not have a high number of subjects or articles on CCA. Using the AQUA tool for anatomical studies, we noted potential bias in result reporting, prompting careful interpretation of our findings. Our research highlights the varied neuropsychological and social presentations of CCA, which can range from normal intellectual functioning to significant psychomotor delays. This aligns with

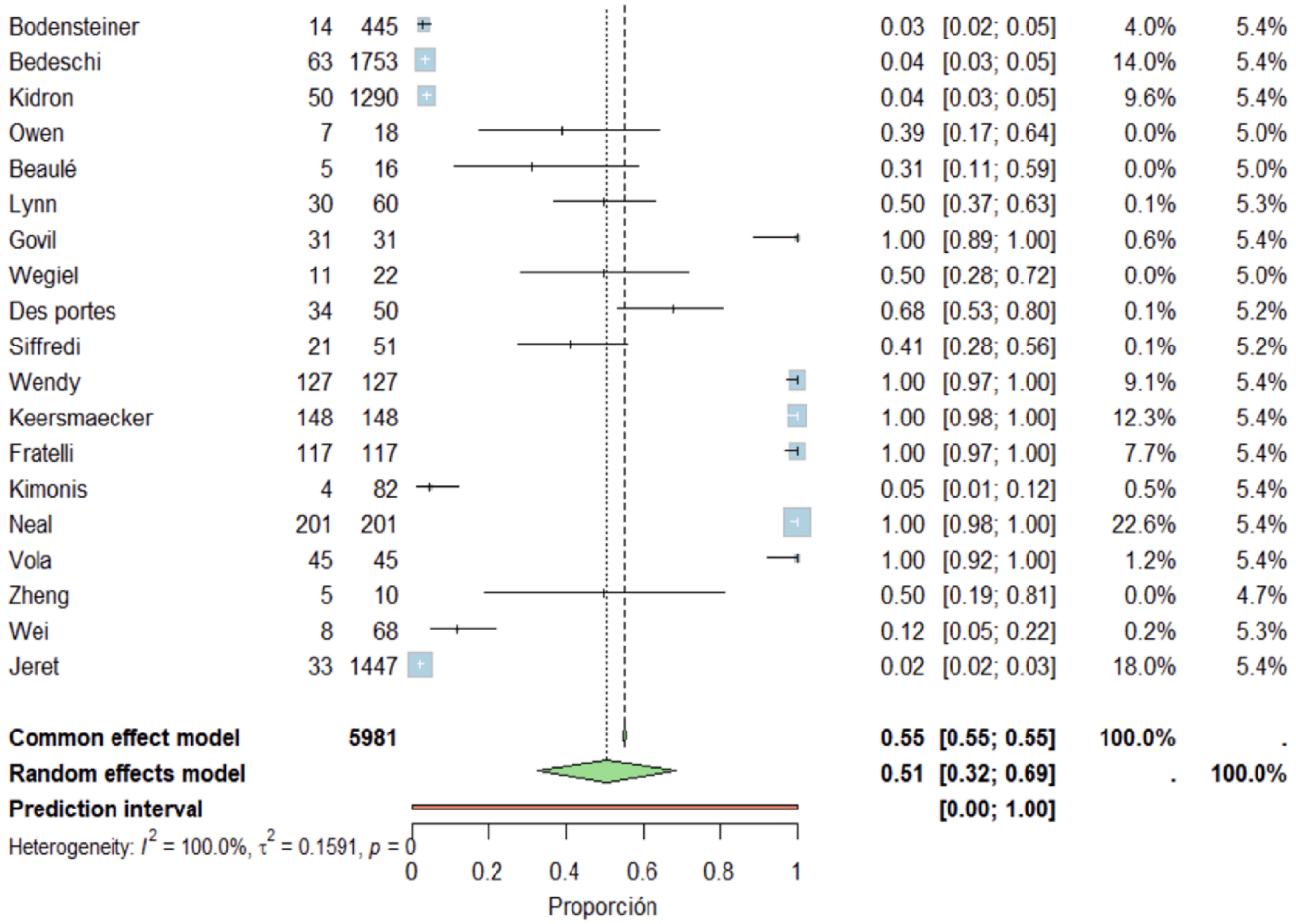

Figure 18. Sensitivity analysis with n less than 10,000.

previous studies showing the highest diagnostic accuracy for CCA in cases linked to extracerebral and CNS anomalies and isolated instances where musculoskeletal malformations are most commonly associated. Clinically, CCA is characterized by considerable variability in its presentation, ranging from almost normal development to significant psychomotor delays. The neuropsychological deficits observed, particularly in learning and memory, seem to be related to issues with information encoding caused by altered interactions. This variability complicates the clinical picture and emphasizes the need for a multidisciplinary approach. The CCA significantly interferes with learning and memory efficiency.[75] This effect could not be related to attention deficit, retention, or retrieval of information, but to problems in encoding information. Studies suggest that difficulties in CCA may be due to altered interhemispheric interactions, affecting the ability to integrate and process visual and auditory information efficiently. Additionally, CCA is linked to various congenital anomalies and malformations of the CNS, including encephalopathies, hemimegalencephaly, and cortical dysplasia, as well as non-neurological issues such as congenital heart disease and limb abnormalities.[15,22]

The high statistical and sampling heterogeneity of the data included meant that several tests should be carried out to see if these factors could influence the results, which from the DOI plot point of view presented low asymmetry, while the publication bias data with the funnel plot were very disparate and highly asymmetric, which indicate that the data provided should be taken with caution even if they are only proportional; finally, the quality of evidence of the data studied fluctuated between very low and moderate, so the subgroup analysis can eliminate some biases and confounding data for a global variable.

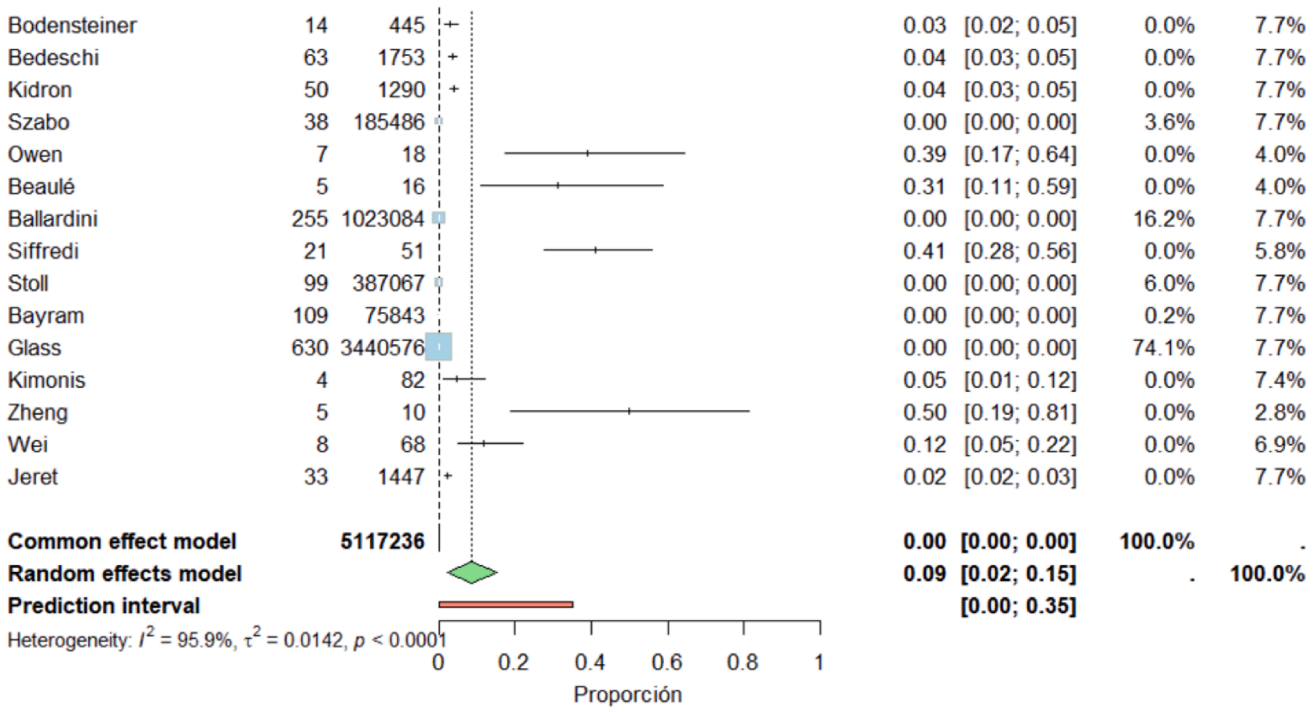

Figure 19. Sensitivity analysis with prevalence less than 50%.

Genetic Relations: Aicardi and Apert Syndromes

CC consists of white matter (myelinated axons) that connects the left and right hemispheres of the brain. It takes on its basic shape after approximately 20 weeks of gestation. During the development of this structure, various changes can occur due to genetic and environmental factors, leading to CCPA or CCCA. CCA is a cranioencephalic malformation characterized by enlarged lateral ventricles and telencephalic hypoplasia, which causes enlargement and displacement of the third ventricle. The etiology of fetal CCA is attributed to genetic factors, prenatal infections, toxic substances, and other elements. About 30% to 45% of fetuses exhibit a defined cause, 10% show chromosomal abnormalities, and 20% to 35% have identifiable genetic syndromes. The accuracy of prenatal diagnosis of CCA has significantly improved due to advancements in prenatal diagnostic technology. An associated characteristic in patients with CCA and Apert syndrome is the presence of syndactyly; intellectual disability and limb malformations are likely manifestations of a multisystem issue. Thus, although this syndrome has additional complications, it should be considered that these subjects will have CCA. Children with Aicardi syndrome (an example of CCA) start to show early onset of seizures, poorer developmental outcomes, and more extensive brain abnormalities on neuroimaging compared to those with nonsyndromic CCA. CCA has been linked to autism spectrum disorders due to limited axonal connections between cortical areas, which may contribute to behavioral issues. The agency's involvement could exacerbate these symptoms.[76] Prenatal diagnosis of CCA can be

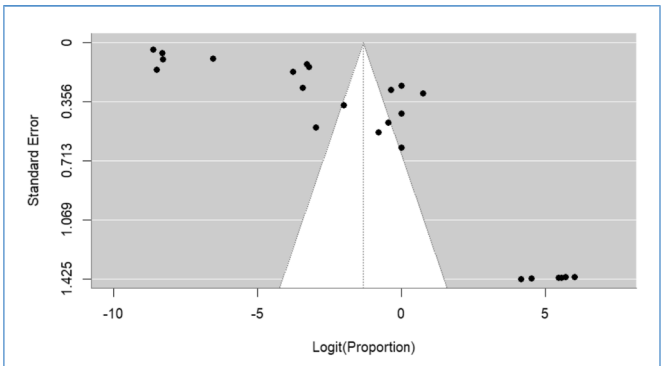

Figure 20. Funnel plot of studies included in the prevalence meta-analysis.

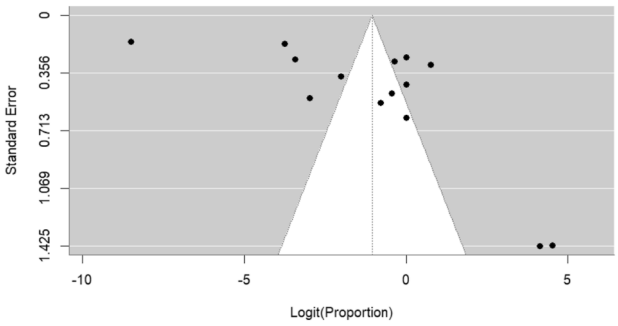

Figure 21. Funnel plot sensitivity analysis with prevalence less than 50%.

complex, particularly in the first trimester, due to phenotypic variability and small structure size.[77] However, advanced neuroimaging techniques such as fetal MRI have significantly improved the ability to detect this condition. Studies suggest that accurate prenatal diagnosis is essential for informed decision-making regarding the continuation of pregnancy, particularly in complex cases of CCA with an increased risk of multiple abnormalities and accelerated deterioration.[78]

Corpus Callosum Complete Agenesis and its Association with Epilepsy

Studies have indicated that CCA frequently presents with symptoms such as intellectual disability, developmental delay, and epilepsy.[41,58] We consider it extremely important to explain the relationship between this last manifestation and the diagnosis of CCA. Epilepsy is defined as a condition characterized by a continuous predisposition to the onset of epileptic seizures due to neurobiological, cognitive, psychological, and social consequences. The CC corresponds to the main band of interhemispheric axonal fibers, thus serving as the major pathway that generalizes the motor manifestations of epilepsy from epileptogenic areas. The diagnosis of CCA should be made through neuroimaging, as this criterion is key to understanding the relationship between epilepsy and the diagnosis of CCA. Some patients with epileptic seizures have undergone emergency imaging studies, revealing the presence of CCA as a possible cause of the epileptic neurological disorder.[61,65]

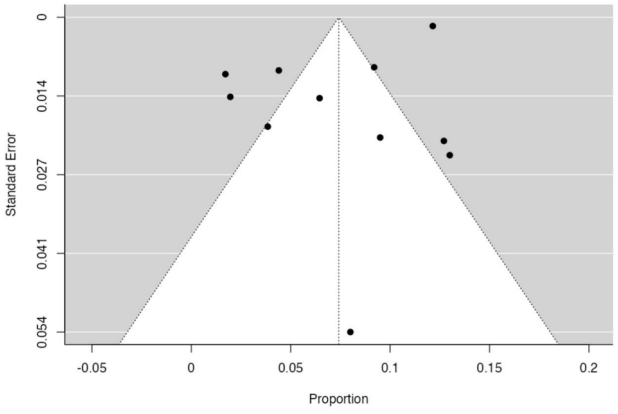

Figure 22. Funnel plot sensitivity analysis with n less than 10,000.

Corpus Callosum Malformations and Mitochondrial Disorders

Mitochondrial disorders, which are caused by mutations in nuclear or mitochondrial DNA, have increasingly been associated with structural brain abnormalities, particularly within the CC. The CC is a significant white matter tract that facilitates communication between the brain hemispheres, and morphological anomalies, such as thinning, hypoplasia, or agenesis, are frequently observed in neurodevelopmental conditions. Disruptions in mitochondrial metabolism adversely affect neural energy homeostasis, leading to a variety of manifestations, including myelination defects, abnormal neuronal migration, and neurodegeneration, all of which can compromise the integrity of the CC. Recent studies elucidate how mitochondrial dynamics, which encompass fusion and fission, membrane integrity, and bioenergetic deficits, contribute to abnormalities in the CC.[79] Al Ojaimi et al. (2022)[80] conducted a review of mitochondrial fission and fusion processes and found that pathogenic dysregulation results in CC thinning, hypomyelination, and brain atrophy. Hofman et al. (2020)[81] conducted a study on CCA that highlighted the role of mitochondrial dysfunction in disrupted neurodevelopment and morphology through oxidative stress and apoptosis. Shamseldin et al. (2022)[82] emphasized mitochondrial dysmorphology as a critical diagnostic feature in variant classification. MRI scans revealed CC abnormalities and defects in the optic pathway. Zhao et al. (2019)[83] highlighted the white matter loss and hypomyelination of the CC due to defects in mitochondrial phosphatidylethanolamine synthesis. Brabbing-Goldstein et al. (2024)[78] found structural brain anomalies, including CCA, attributable to impaired mitochondrial complex I function.

Diagnosis and Clinical Management for Patients with Corpus Callosum Agenesis

The prognosis for individuals with CCA can vary significantly. Some patients, especially those with isolated CCA, may experience relatively normal development. In contrast, others may encounter challenges with language, behavior, and motor skills, which often become apparent by school age. CCA is typically associated with reduced connectivity between the

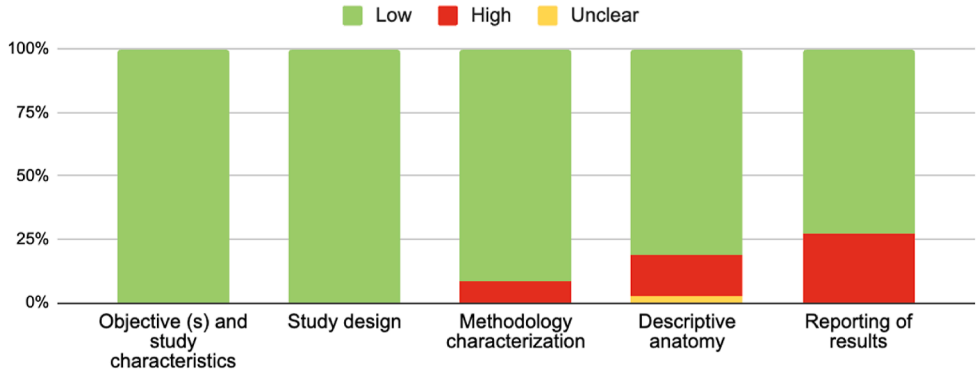

Figure 23. Bias risk analysis using the AQUA checklist tool for anatomical studies included in the systematic review. AQUA, Anatomical Quality Assessment.

brain's hemispheres, which can account for difficulties in verbal fluency and other cognitive functions (De Zhao, 2020). Current research explores individual differences in brain connectivity and their impact on clinical and developmental outcomes over time.[84] Lesions of the CC can be reversible or irreversible. Reversible lesions, such as reversible splenic lesion syndrome and mild encephalitis/encephalopathy with a reversible splenic lesion, are usually associated with viral infections (such as influenza and rotavirus) or seizures and have a favorable prognosis with complete recovery within a few weeks. On the other hand, irreversible lesions, such as those caused by metabolic and neurodegenerative disorders (e.g., adrenoleukodystrophy and metachromatic leukodystrophy), cause persistent damage to the spleen, which may worsen the clinical picture of CCA presence.[84] CC cytotoxic lesions have also been associated with various diseases. These lesions, primarily visible on MRI, are characterized by T2 and FLAIR hyperintensity (areas on MRI that appear brighter than the surrounding tissues), T1 hypointensity, diffusion restriction, and lack of gadolinium enhancement. Although they usually involve the spleen, they may extend to other regions. They are associated with viral infections (e.g., COVID-19 and influenza), drug use or withdrawal (especially antiepileptic drugs), metabolic disorders, and trauma. Although most of these lesions are transient, in rare cases, they may persist, probably due to cytotoxic edema resulting from excitotoxicity and cytokine activation. It can be concluded that the CCA presence may make this condition worse.[44] CC infarcts, primarily located in the splenium, are linked to the blood supply from the posterior cerebral artery. Clinically, they can lead to symptoms such as weakness, sensory disturbances, and, in rare instances, callosal disconnection syndrome, characterized by phenomena like alien hand syndrome. Common risk factors for these infarcts include hypertension, dyslipidemia, and diabetes mellitus. While the double irrigation of the CC and its dense white matter structure makes it less vulnerable to ischemia, the presence of CCA disease may worsen this condition.[62,73] The variable prognosis of CCA presents challenges in clinical management, underscoring the importance of personalized treatment plans and long-term follow-up. Future research focusing on the relationship between brain connectivity and clinical outcomes will be crucial for improving our understanding and management of this condition. The precision of prenatal diagnosis for CCA through US is essential given that CCA significantly influences neurological development and interhemispheric functional integration. A meta-analysis indicates that prenatal US possesses moderate sensitivity (0.72) and high specificity (0.98) for detecting CCA.[55] This suggests that while the US effectively confirms suspected cases, there is significant room for improvement in early detection, especially for subtle variations. CCA can be classified as complete or partial, with partial forms posing greater diagnostic challenges. Early identification is crucial for assessing prognosis. In some cases, patients with CCA may have normal development with mild neuropsychological deficits. However, CCA can also be linked to more severe conditions, such as Aicardi syndrome or autism spectrum disorders. Using US and other prenatal imaging techniques, like fetal MRI, is essential for detecting complex cases and informing parents of potential risks. While the US has high specificity, its moderate sensitivity can lead to false negatives, delaying CCA identification and impacting clinical planning. Incorporating neurosonography and fetal MRI when suspected anomalies are present is advisable to enhance diagnostic accuracy. Further research on the variability of CC morphological anatomy is necessary to understand the factors influencing these variants and their progression.

Limitations

This review has encountered several limitations stemming from biases related to publication and authorship within the included studies. First, studies yielding

conflicting results that were published in nonindexed literature outside of the selected databases may have been overlooked. Second, there may be limitations regarding the sensitivity and specificity of the search methods employed. Finally, the authors personally selected the articles for inclusion in this review. Regarding the search carried out in Google Scholar, which included some predatory and low-quality journals, we exhaustively reviewed the studies that were not duplicated in the other databases, leaving 2 readable studies, which after reading the full text were eliminated due to flaws in the methodological processes and data grouping. These factors elevate the risk of excluding potential cases from countries beyond Asia and North America, which may not be adequately represented in the scientific community. Furthermore, the subgroup analysis did not meet the minimum requirement of 4 studies per group (Fu et al. 2011).

CONCLUSION

CC morphological variants occur in a small percentage of the population, with CCCA being one of the most frequently described variants. Early diagnosis, particularly during the fetal stage, is essential as it allows specialists to implement more effective treatments and potentially reduce the risk of neurofunctional changes. Moreover, a thorough understanding of the morphological characteristics of CCA can lead to accurate early diagnosis, thereby eliminating the need for differential diagnoses that may disrupt the function of interhemispheric connections and the brain's overall functional connectivity. Familiarity with clinical presentations can also significantly improve the speed and effectiveness of diagnosis and treatment for patients with this anatomical variant. Additionally, there is a compelling need for further research into neurophysiological approaches and the unique features of CCA. Such investigations could significantly enhance our anatomical and clinical understanding of this condition. After analyzing the prevalence data on CCA, it was determined that the evidence on the presence of CCA in different modalities, such as CCCA or CCPA, in different populations has low certainty according to Grading of Recommendations, Assessment, Development and Evaluation. Given this relationship, our results should be viewed with caution, and further research is encouraged to improve the certainty of the evidence and confirm the present results on CCA.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Juan José Valenzuela-Fuenzalida: Conceptualization, Funding acquisition, Methodology, Resources, Supervision. **Sebastián Orellana-Hidalgo:** Conceptualization, Methodology, Software, Validation. **Vicente Baeza-Garrido:** Data curation, Formal analysis, Funding acquisition. **Martin Trujillo-Riveros:** Data curation, Formal analysis, Investigation, Methodology. **Isidora Aguilar-Aguirre:** Investigation, Methodology, Resources, Software. **Pablo Nova-Baeza:** Conceptualization, Investigation, Methodology. **Mathias Orellana-Donoso:** Conceptualization, Data curation, Resources, Software. **Gloria Cifuentes-Suazo:** Investigation, Validation, Visualization, Writing — original draft, Writing — review & editing. **Alejandro Bruna Mejias:** Funding acquisition, Investigation, Methodology, Software. **Daniel Casanova-Martinez:** Formal analysis, Methodology, Resources, Visualization. **Juan Sanchis-Gimeno:** Supervision, Validation, Visualization, Writing — original draft, Writing — review & editing. **Maria Piagkou:** Validation, Visualization, Writing — original draft, Writing — review & editing. **George Triantafyllou:** Methodology, Validation, Visualization, Writing — review & editing. **Marko Konschake:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Validation, Writing — original draft, Writing — review & editing.

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