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REVIEW

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Anatomical variations of the circle of Willis and their prevalence, with a focus on the posterior communicating artery: A literature review and meta-analysis

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Abstract

The circle of Willis is an anastomotic network of arteries surrounding the base of the brain, providing collateral circulation to prevent ischemia. It has, however, long been established that it exhibits considerable anatomical variation when compared to Thomas Willis' originally described circle. This study aimed primarily to determine an accurate prevalence of the variation of the circle of Willis in the general population and the prevalence of common posterior communicating artery variations. Additional aims were to explain why such a wide range of reported variations exist, and whether different types of studies report significantly different prevalence of variation. A comprehensive literature search identified 764 papers. A three-phase screening process was undertaken, involving a critical analysis of papers, and a total of 33 papers were selected for analysis and literature review. A descriptive statistics test with bootstrap was performed to estimate the average prevalence of variations. The estimated prevalence of general variation, unilateral, and bilateral posterior communicating artery hypoplasia or aplasia was 68.22 ± 14.32%, 19.45 ± 8.63%, and 22.83 ± 14.58%, respectively. Over half of the population exhibit a circle of Willis with some form of variation. To provide a more accurate estimation for the prevalence of variations, a universal classification system needs to be established, collating all the work from high-quality studies, to provide a comprehensive database of the circle's variations. Knowing the prevalence of variations and how they can impact neurosurgical approaches or patterns of ischemic pathology can be crucial in providing effective patient care.

KEYWORDS

cerebral arterial circle, circle of Willis, communicating, hypoplasia, posterior, variation

1 | INTRODUCTION

The circle of Willis (CoW) is an anastomotic arterial network on the base of the brain. Its major role is to provide efficient collateral circulation to cerebral and cerebellar tissue to prevent ischemia, and subsequent transient ischemic attack or stroke (Karatas, Coban, Cinar, Oran, & Uz, 2015; Karatas, Yilmaz, Coban, Koker, & Uz, 2016; Klimek-Piotrowska et al., 2016). First described in Thomas Willis' landmark work *"Cerebri Anatome"* (Willis, 1664), the CoW is classically described as a symmetrical polygon, derived from anastomoses between branches of the internal carotid arteries and vertebral arteries. Modern anatomy textbooks refer to it as a roughly pentagonal circle of vessels on the ventral surface of the brain (Moore, Dalley, & Agur, 2014). It consists of anterior and posterior cerebral arteries, providing arterial supply to the various lobes of the cerebrum and cerebellum. An anterior communicating (AComA) and two posterior communicating (PComA) arteries join these cerebral arteries and help form the collateral arterial network (Moore et al., 2014; Standring & Gray, 2016) (Figure 1).

The CoW is an eponymous term, with several synonyms used throughout the literature. Whilst "circle of Willis" is the most widely utilized term, (and hence, the term used throughout this article), other common synonyms are "*Cerebral Arterial Circle*," or "*Circulus Arteriosus Cerebri*," which are the terms used in Terminologia-Anatomica (Federative Committee on Anatomical Terminology, 1998), and utilized by several studies (Eftekhar et al., 2006; Ardakani et al., 2008). Another synonym within the literature is "Arterial circle of the Brain" (Lazorthes, Santini, & Salamon, 1979).

Since Willis first described it, the CoW has been examined in cadaveric studies and analyses of live patient imaging (LPI), including computed tomography (CT) and magnetic resonance angiography (MRA). Although the CoW, as classically described, is symmetrical, with vessels of an approximately equal diameter bilaterally, it is subject to significant morphological variation. Unfortunately, the multiplicity of anatomical studies of the CoW has not helped to clarify the prevalence of its morphological variation, primarily because of the inconsistency between their outcomes. Studies report a classical CoW to be present anywhere from 4.8% (Fisher, 1965) to 85.4% (Yeniçeri, Çullu, Deveer, & Yeniçeri, 2017) of the population. This wide range of

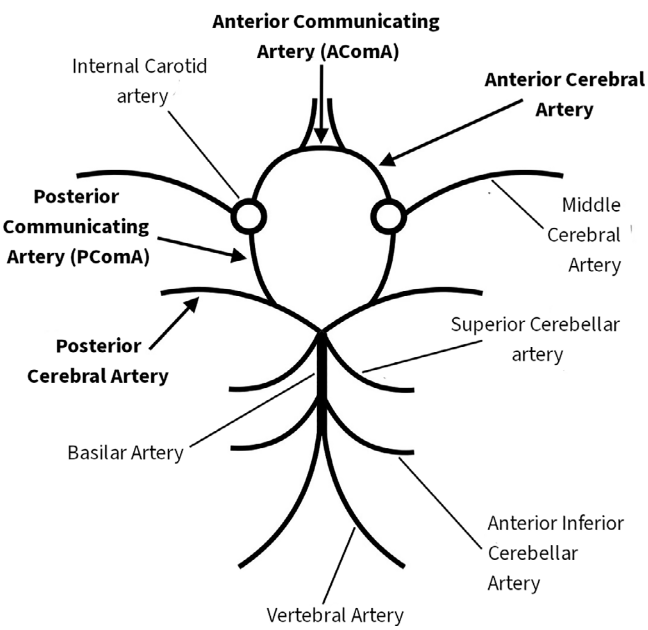

FIGURE 1 The original Circle of Willis, as described by Thomas Willis in 1664 (Original image). The anterior and posterior cerebral arteries, AComA, and PComA, which are integral to the circle of Willis, are highlighted

reported rates of variation has been proposed as being due to differing methodology or nomenclature between studies (Karatas et al., 2016), ethnic and population discrepancies (DeSilva, Silva, Amaratunga, Gunasekera, & Jayesekera, 2011; Eftekhar et al., 2006; Karatas et al., 2016), and whether a neurologically healthy or diseased population were studied (Kayembe, Sasahara, & Hazama, 1984; Riggs, 1963). The literature can, however, agree on one thing: variation is most commonly seen in the PComA (Riggs, 1963; Fisher, 1965; Lazorthes et al., 1979; Eftekhar et al., 2006,).

For clinicians performing procedures on the CoW, extensive knowledge of its anatomy and potential variations is essential. Understanding common variations, how they impact clinical practice, and the risks of ischemic events are necessary to provide effective and safe care for patients (Zhou et al., 2016).

In this study, a systematic literature review and meta-analysis of published research examining variations of the CoW was performed with the following aims: (a) to suggest a more accurate range for the prevalence of variations of the CoW within the general, neurologically healthy population, (b) to establish an estimated prevalence for the most common types of variation (PComA), (c) to review why such a large discrepancy in the reported prevalence of CoW variation exists, and (d) establish whether a significant difference exists between the results of cadaveric and LPI studies.

2 | MATERIALS AND METHODS

A Medline search was carried out, in July 2017, using two Medical Subject Headings (MeSH). The first related to the CoW, incorporating all used synonyms: *"circle of Willis OR Cerebral Arterial Circle OR Circulus Arteriosus Cerebri OR Willis"? circle'* ('?' denotes wildcard character). The second related to variations: *"varia*OR atypical OR abnormal*OR anomal*OR unusual OR incomplete"* ('*' denotes truncation). These search terms were combined with the Boolean operator "AND". This search resulted in 764 studies that underwent a three-phase screening process.

2.1 | Three-phase screening process

A summary of the screening and appraisal process is shown in Figure 2. In Phase One, all studies with the MeSH terms in their titles were selected. The abstracts of all the selected articles were scrutinized, and inclusion and exclusion criteria applied (Table 1). Inclusion criteria included a title referencing the CoW (or synonyms) or variation, and an abstract or title relevant to one of this study's aims. Studies examining *only* fetal specimens or neurologically unhealthy populations were excluded. Exclusion criteria also included case reports, animal studies, or studies focusing on an accessory vessel of the CoW (e.g., recurrent artery of Heubner). One hundred and twenty-nine studies were identified as appropriate for Phase Two screening and were categorized into cadaveric or LPI-based studies, and whether they examined the full or partial CoW

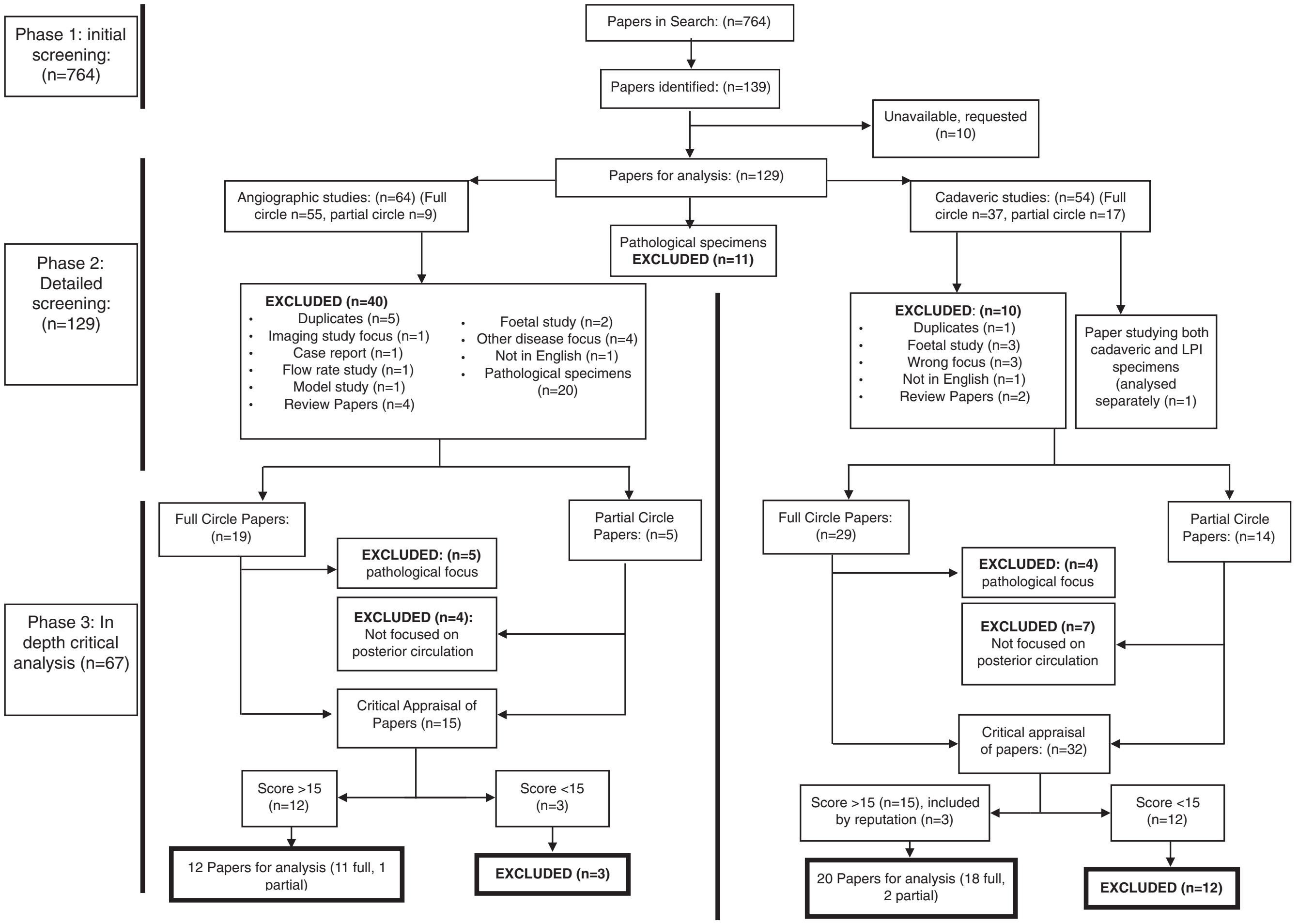

FIGURE 2 A flow diagram summarising the three phase screening process of the literature search, screening and appraisal. (Original image)

TABLE 1 Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
• Title contains a term corresponding to MeSH term for 'CoW' or 'variation' • Abstract and title deemed relevant to one of the study's aims • The study examines a healthy population, or population with cerebral ischemia, or study compares a healthy and diseased population. • Paper is available in the English language • Paper studied non-fetal specimens/subjects	• Case reports, editorials and letters • Animal studies • Model/computer-generated brain studies • Focused on flow patterns or blood distribution patterns • Paper focused on a specific examination of an accessory vessel, not in the main CoW (e.g., recurrent artery of Heuber). • Fetal studies (with no adult control) • Studies comparing imaging or cadaveric preservation methods

In Phase Two, the inclusion and exclusion criteria were applied, whilst reading the introduction, methodology, and conclusion of each article. Studies were excluded for irrelevant focus such as blood flow rates (van-Raamt, Mali, van-Laar, & van der Graff, 2006), the effect of variations on diseases, such as migraine (Henry et al., 2015), or the use of artificial models of the CoW (Nowinski et al., 2009). Forty-three cadaveric studies and 24 LPI studies were identified as appropriate for Phase Three.

In Phase Three, a detailed analysis of each article was undertaken, and a further 11 cadaveric and 9 LPI studies were excluded, based on a thorough examination against the inclusion and exclusion criteria. For studies examining partial CoWs, only those examining the posterior cerebral arteries or PComA were included (this is the region most commonly exhibiting variation, and examining other specific areas of the circle was beyond the scope of this review).

2.2 | Critical appraisal

The remaining 32 cadaveric and 15 LPI studies underwent a critical appraisal, to assess the quality of research, and to determine whether they were suitable for further review and meta-analysis. The critical appraisal used a bespoke scoring system, based on the Critical Appraisal Skills Programme (CASP) criteria for Cohort and Case–Control Studies (Critical-Appraisal-Skills-Programme, 2017a, 2017b).

TABLE 2 Summary of studies analyzed. Grey boxes represent values not reported by the study

Study and location	Sample size	Specimen type and health	Hypoplasia definition	Typical CoW % (n)	Variant CoW % (n)	Hypoplastic PComA % (n)	Aplastic PComA % (n)	Classification system used?	Most common variation
	Cadaveric studies								
(Al-Hussain, Shoter, & Bataina, 2001) (Jordan)	50	No cerebrovascular disease (CeVD)	<1 mm	20% (10)	80% (40)	Overall 33% (33).[a]	13% (13).[a]	Own	PComA hypoplasia
(Alpers, 1963) USA	350	Healthy control group	<1 mm	52% (182)	48% (168) •	Unilateral 8%, bilateral 6%	NA	Own	PComA abnormality
(Ardakani et al., 2008) Iran	30	Infants and fetuses, no CeVD.	<0.6 mm	42.1% (12)	57.8% (18)	Unilateral 43% (13) Bilateral 8% (2).[a]	Unilateral 19.9% (6) Bilateral 3.3% (1)[a]	Own	PComA hypoplasia
(Battacharji & Hutchinson, 1967) UK	88	Healthy control group.	<1 mm	NA	NA	Overall 39% (34).[a]	NA	Unknown	PcomA hypoplasia
(DeSilva et al., 2011; DeSilva, Silva, Gunasekera, & Jayesekera, 2009) Sri-Lanka	225	No CeVD	<1 mm	14.2% (32)	85.8% (193)	Unilateral 11.5% (26), bilateral 23% (52)	NA	Lazorthes	PComA hypoplasia (bilateral)
(Eftekhar et al., 2006) Iran	102	No CeVD	<1 mm	28% (29)	71.6% (73)	Unilateral 27%, bilateral 33%	Unilateral 7%, bilateral 3%	Lazorthes	PComA hypoplasia (bilateral)
(Fisher, 1965) USA	414	Unselected, no exclusion of CeVD	<1 mm	4.8% (20)	95.2% (394) •	Unilateral 6% (24), bilateral 30.4% (126)	NA	Own	PComA hypoplasia (bilateral)
(Hashemi, Mahmoodi, & Abbas, 2013)Iran	200	No CeVD	<1 mm	34.5% (69)	65.5% (131)	Unilateral 17.5% (37), bilateral 24% (48)	Unilateral 3% (6), bilateral 1% (2)	Own	PComA hypoplasia (bilateral)
(Kapoor, Singh, & Dewan, 2008) India	1,000	No CeVD	<1 mm	45.2% (452)	54.8% (548)	Unilateral 13.1% (131) Bilateral 3.6% (36)	Unilateral 0.9% (9), bilateral 0.1% (1)	Own	PComA hypoplasia (unilateral)
(Karatas et al., 2016) Turkey	100	No CeVD	<1 mm	8% (8)	92% (92)[b]	Unilateral 24% (24), bilateral 37% (37)	NA	Own	PComA hypoplasia (bilateral)
(Kayembe et al., 1984) Japan	148	Healthy control group.	<1 mm	46.3% (62)	53.7% (86)	Overall 8.3% (11).[a]	6% (8).[a]	Own	X-ACA
(Klimek-Piotrowska et al., 2016) Poland	100	No CeVD	<1 mm	27% (27)	73% (73)	Unilateral 11% (11), bilateral 16% (16)	NA	Lazorthes	PComA hypoplasia (bilateral)
(Lazorthes et al., 1979) France	200	Unspecified	Not given	14.5% (29)	85.5% (171)	Unilateral 14% (28), bilateral 22% (44)	NA	Own	PComA hypoplasia (bilateral)

(Continues)

TABLE 2 (Continued)

Study and location	Sample size	Specimen type and health	Hypoplasia definition	Typical CoW % (n)	Variant CoW % (n)	Hypoplastic PComA % (n)	Aplastic PComA % (n)	Classification system used?	Most common variation
(Papantchev et al., 2007) Bulgaria	99	No CeVD	<1 mm	57.6% (57)	42.4% (42) •	Overall 27.3% (27) (unique classification).	NA	Own	PComA abnormality
(Riggs, 1963) USA	994	Neural dysfunction	Not given	19.2% (192)	80.6% (802)	Unilateral 8.9% (88), bilateral 12.7% (126).[a]	NA	Unknown	PComA hypoplasia (bilateral)
(Siddiqi, Tahir, & Lone, 2013) Pakistan	51	Unspecified	<1 mm	29.4%	70.6%	Overall 33.3%[a]	Unilateral 15.6%, bilateral 7.8%	Own	PComA hypoplasia
(Saikia, Handique, Phukan, Lynser, & Sarma, 2014) India	70	No CeVD	<1 mm	20%	80%	Unilateral 18.6%, bilateral 14.3%	NA	Own	Fetal PComA
(Idowu, Malomo, & Akang, 2010) Nigeria	50	Meningitis and atherosclerosis excluded	Not given	56%	44% •	Overall 22%	NA	Own	PComA hypoplasia
(Saha, Sarkar, & Mandal, 2015) India	56	No CeVD, male-only	<0.5 mm	NA	NA	NA	NA	Own	Fetal PComA
	LPI studies								
(Chen et al., 2004) Taiwan	507	3D-TOF-MRA, no CeVD	<0.8 mm	21.30%	78.70%	Unilateral 12.03%, bilateral 42.8%•. Included absence.		Own	PComA hypoplasia/ absence (bilateral)
(El-Barhoun, Gledhill, & Pitman, 2009) Australia	171	MRA and MRI neurological patients	<0.8 mm	32.2% (55)	67.8% (116)	Unilateral 10% (17), bilateral 10.5% (18). Included absence		Krabbe-Hartkampe	PComA hypoplasia
(Karatas et al., 2015) Turkey	100	CTA. No CeVD.	<1 mm	28% (28)	72% (72)	Unilateral 15% (15), bilateral 5% (5)	Unilateral 15% (15), bilateral 1% (5)	Own	PComA hypoplasia/ absence (unilateral)
(Klimek-Piotrowska et al., 2013) Poland	250	CTA. No CeVD	Not given	16.8%	83.2%	Unilateral 9.20%, bilateral 4.80%	Unilateral 26%, bilateral 29.2%	Lazorthes	PComA absence (bilateral)
(Krabbe-Hartkamp et al., 1998) Netherlands	150	3D-TOF-MRA. Some neurologically unhealthy.	<0.8 mm	42%	58%	Unilateral 28.7%, bilateral 10.7%. Includes absence.		Own	PComA hypoplasia/ absence (unilateral)
(Li et al., 2011) China	160	3D-TOF-MRA. No CeVD	<1 mm	27% (42)	73% (118)	Unilateral 9.4% (15), bilateral 13.8% (22)	Unilateral 10% (16), bilateral 33.1% (53) •	Own	PComA absence (bilateral)

TABLE 2 (Continued)

Study and location	Sample size	Specimen type and health	Hypoplasia definition	Typical CoW % (n)	Variant CoW % (n)	Hypoplastic PComA % (n)	Aplastic PComA % (n)	Classification system used?	Most common variation
(Macchi et al., 2002) Italy	118	3D-TOF-MRA. Healthy older patients	<0.8 mm	47%	53%	Unilateral 12.7% (15), bilateral 14.4% (17). Includes absent		Own	PComA hypoplasia/ absence (bilateral)
(Malamateniou et al., 2009), UK	65	3D-TOF-MRA. Infants, no CeVD.	Not given	41.5%	58.5%	Overall 30%, includes absent.		Own	PComA hypoplasia/ absence
(Naveen, Bhat, & Karthik, 2015) India	300	3D-TOF-MRA. Neuroischemia referrals.	<0.8 mm	16.6% (50)	83.4% (250)	Unilateral 9%, bilateral 32.7%. Includes absence		Chen's (2004, Taiwan, above)	PComA hypoplasia/ absence (bilateral)
(Qiu, Zhang, Xue, Jiang, & Zhang, 2015) China	2,246	3D-TOF-MRA and MRI. No CeVD	Dependent on artery average	7.57% (170)	92.43% •	Unilateral 22.8% (512), bilateral 47.5%[b] (1066). Includes absence		Own	PComA hypoplasia/ absence (bilateral)
(Saikia, Handique, Phukan, Lynser, & Jamil, 2014) India	70	3D-TOF-MRA. No CeVD.	<1 mm	24.28% (17)	75.72%	Unilateral 20% (14), bilateral 11.4% (8)	Unilateral 1.4% (1), bilateral 7.1% (5)	Own	Fetal PComA
(Voljevica & Kapur, 2005) Bosnia	150	MRA. No CeVD	Not given	NA	NA	Unilateral 26.7% (40), bilateral 8.7% (13)	NA	Own	PComA hypoplasia (unilateral)
(Papantchev et al., 2013) Bulgaria	250	CTA, no CeVD.	<1 mm	41.4%	58.6%	Unilateral left only: 35.6%	NA	Own	PComA hypoplasia, unilateral

Abbreviations: 3D-TOF-MRA, 3D time of flight magnetic resonance angiography; CeVD, cerebrovascular disease; CTA, computerized tomography angiography; MRI, magnetic resonance imaging; NA, no data available.

[a]Results did not clearly state whether they were reporting PComA hypoplasia/aplasia as the only variation, or as hypoplasia/aplasia in the presence of another, separate variation (co-variation).

[b]Result is considered an extreme value, outside the *SD* of the results of the present study.

The CASP criteria were modified to make them more relevant to this review and to focus on specific elements, such as the inclusion of specific definitions of the classical CoW, and the provision of specific definitions for hypoplastic vessels. Studies were further scored in six separate categories: addressing a clearly-focused issue, appropriate methodology, appropriate subject/specimen recruitment, minimization of bias and confounding factors, clear reporting of results, and acknowledgment of limitations. A score of >15 out of 24 points was required for a study to undergo further analysis and review. Papers scoring 15 or less were considered to have a less robust methodology or less reliable results. Studies scoring >15 underwent a reference screen to identify other potentially relevant studies, of which the inclusion and exclusion criteria were then applied. One study (Gunnal, Farooqui, & Wabale, 2014) was found in the reference screen, but scored <15 and was excluded. The previously mentioned study that reported 85.4% (Yeniçeri et al., 2017) prevalence of a classical CoW did not score sufficiently highly on the critical appraisal and thus was not included in the analysis.

Three papers, by Riggs, 1963, Fisher (1965) and Lazorthes et al. (1979) scored <15 on the critical appraisal, but were still included in the literature review on the basis that their work is heavily referenced throughout the literature, and are considered landmark studies of CoW anatomy. Notably, Lazorthes et al. (1979) created a well-known classification system of variant CoWs. Hence, it was considered inappropriate to exclude these studies from the literature review. However, since they do not explicitly meet the inclusion criteria, their findings were interpreted with caution and excluded from the meta-analysis.

2.3 | Extracted data

Twenty cadaveric studies, 12 LPI studies, and one study utilizing both cadavers and LPI (Papantchev et al., 2013) passed critical appraisal and underwent a literature review. However, only 17 cadaveric, 12 LPI, and one combined cadaveric and LPI study underwent meta-analysis, following exclusion of Riggs, 1963, Fisher (1965), and Lazorthes et al. (1979), as described above. From each paper, data were extracted and recorded (Table 2), including sample size and the overall percentage prevalence of typical and variant CoWs. The estimated prevalence of PComA variations was also recorded (hypoplasia or aplasia). Some studies reported the prevalence of PComA hypoplasia and aplasia as separate values, and these were combined for analysis, allowing comparison between studies.

2.4 | Statistical analysis

To establish an estimated prevalence of variation, all data underwent descriptive statistical testing, with a 5,000 bootstrap. A comparison of sample sizes against the reported prevalence of variation was analyzed for clusters and outliers to determine if there was a reported sample size above which results may be considered reliable.

Independent samples *t*-test was performed on IBM SPSS Statistics (2015), to establish whether there was a significant difference in the prevalence of variation reported in cadaveric or LPI studies.

3 | RESULTS

Thirty-three studies were included in the final review and analysis. Riggs (1963), Fisher (1965) and Lazorthes et al. (1979) were included in the literature review by reputation but were excluded from the meta-analysis, on the basis that they did not meet the minimum score on the critical appraisal. Studies examined were published between 1965 (Fisher, 1965) and 2016 (Karatas et al., 2016; Klimek-Piotrowska et al., 2016), with sample sizes ranging from 30 (Ardakani et al., 2008) to 2,246 (Qiu et al., 2015). Definitions of a hypoplastic vessel varied between studies: some defined it as a vessel <1 mm diameter (n = 18) and others did not provide a definition (n = 6). The extracted data are summarized in Table 2.

Scatter graphs were created to illustrate the differences in the reported prevalence of variant CoWs in general (Figure 3), and the prevalence of both unilateral (Figure 4) and bilateral (Figure 5) hypoplastic or aplastic PComAs. It was not possible to estimate the minimum sample size a study would need to produce results considered reliable, due to a wide range of reported prevalence and no clear clusters appearing in the scatter graphs. Thus, no study was excluded based on their sample size. The smallest was 30 and this could be considered as a reasonable lower boundary for future work in this field.

3.1 | Prevalence of general variation of the CoW in a neurologically healthy population

Twenty-six studies reported the prevalence of a variant CoW in their sample (Figure 3), ranging between 42.4% (Papantchev et al., 2007) to 95.2% (Fisher, 1965). No significant difference was found between the reported prevalence of variation in cadaveric and LPI studies, $t(26) = -0.981$, $p = .25$. Therefore, the reported prevalence from both cadaveric and LPI studies was analyzed together. The average (mean) prevalence of variation of the CoW within a healthy population was 68.22% ± 14.32% (*SD*). The most frequently reported prevalence of variation was in the range of 71–80% (n = 8); 88.5% of studies analyzed reported the prevalence of a variant CoW as >51%.

3.2 | Prevalence of PComA variation (hypoplasia and aplasia)

Nineteen studies were included in the analysis to determine the prevalence of unilateral and bilateral PComA hypoplasia or aplasia (Figures 4 and 5). Only studies that reported PComA hypoplasia or aplasia as the only variation (i.e., not coexisting with other variations) were included. This ensured that the cases of PComA described could be reliably considered similar and comparable. The examination of

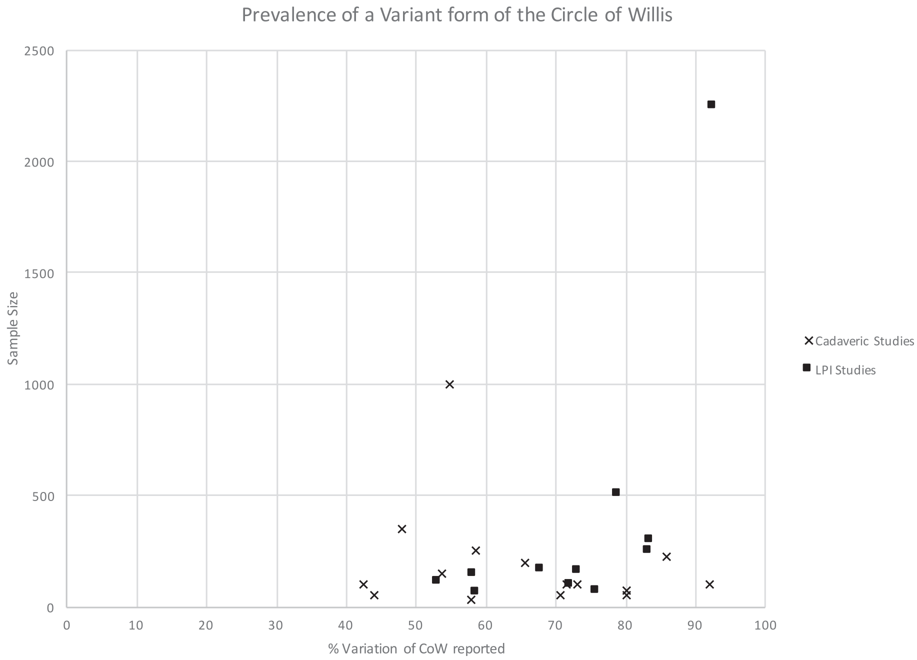

FIGURE 3 Prevalence of a variant form of the Circle of Willis (n = 26). Variation is reported between approximately 42% and 92%, and a wide range of reported prevalence of variation can be seen. Cadaveric and LPI studies overlap, and no obvious difference can be seen between them

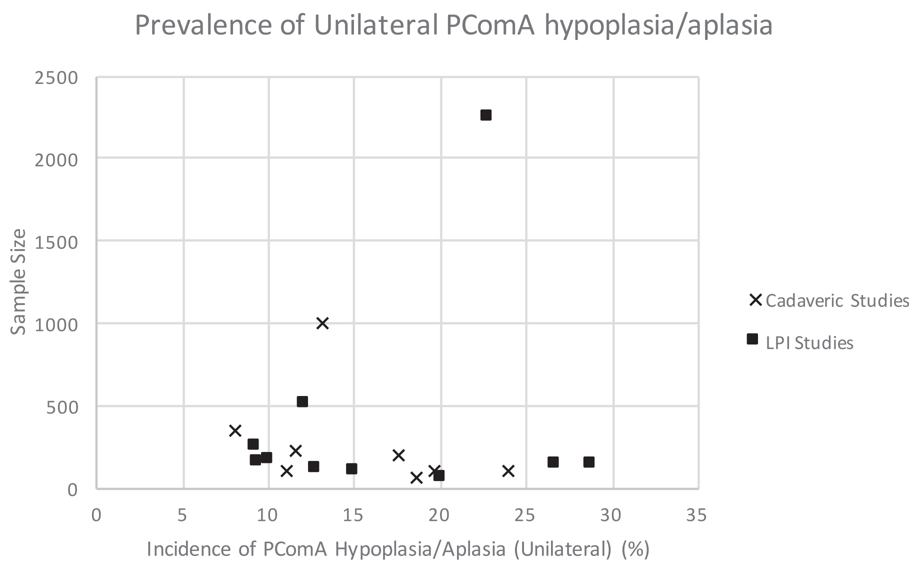

FIGURE 4 Prevalence of unilateral PComA hypoplasia (n = 19). A wide range of prevalence of hypoplasia is reported, from approximately 8% to 28%. Cadaveric and LPI studies overlap, and no obvious difference can be seen between them

CoWs with multiple variations was beyond the scope of the present study. Both the prevalence of hypoplasia and aplasia were combined into a single value to allow comparison between studies that reported them as such.

The range of prevalence of unilateral PComA hypoplasia or aplasia (Figure 4) reported was 8% (Alpers, 1963) to 28.7% (Klimek-Piotrowska et al., 2013). There was no significant difference between the reported prevalence in cadaveric and LPI studies ($t[17] = -0.74$, $p = .72$), thus their data were analyzed together. The mean prevalence of unilateral PComA hypoplasia and aplasia was 19.45% ± 8.63%. The modal group was 10.1–15%, (n = 6).

The range of prevalence of bilateral PComA hypoplasia and aplasia (Figure 5) reported was 3.7% (Kapoor et al., 2008) to 47.5% (Qiu et al., 2015). There was no significant difference between the prevalence reported in cadaveric and LPI studies, ($t[17] = -0.68$, $p = .124$) thus their data were analyzed together. The mean prevalence of bilateral PComA hypoplasia or aplasia was 22.83% ± 14.58%. The range of prevalence reported was widely distributed (Figure 5), and no clear modal group could be defined.

3.3 | Differences between the results of cadaveric and LPI studies

As highlighted above, independent samples t-tests showed no significant difference between the prevalence of variation reported in cadaveric and LPI studies, in general variation or PComA variation. On visual examination of the scatter graphs (Figures 3, 4, and 5), there is a significant overlap between the two types of study, with no discernible pattern or correlation between them.

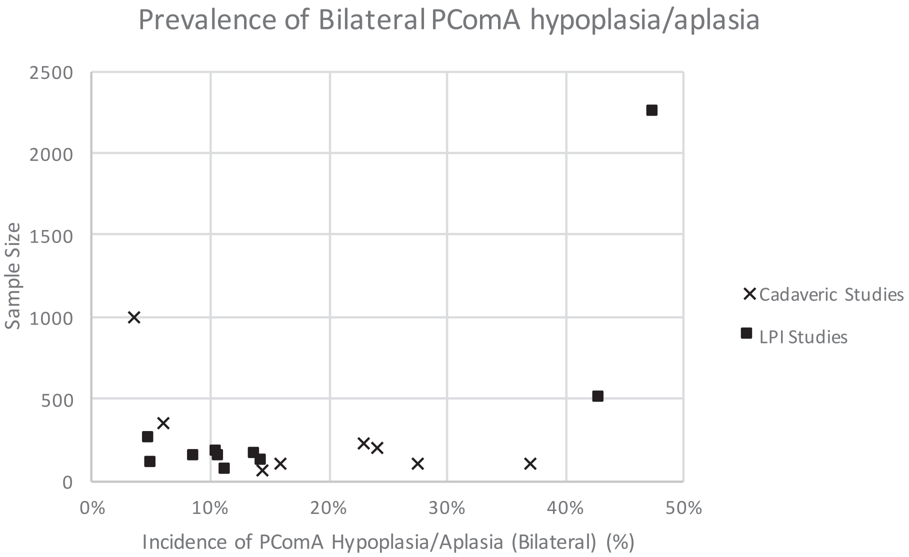

FIGURE 5 Prevalence of bilateral PComA hypoplasia/Aplasia (n = 19). There is a wide range of reported prevalence of hypoplasia and aplasia. No significant difference exists between cadaveric and LPI studies

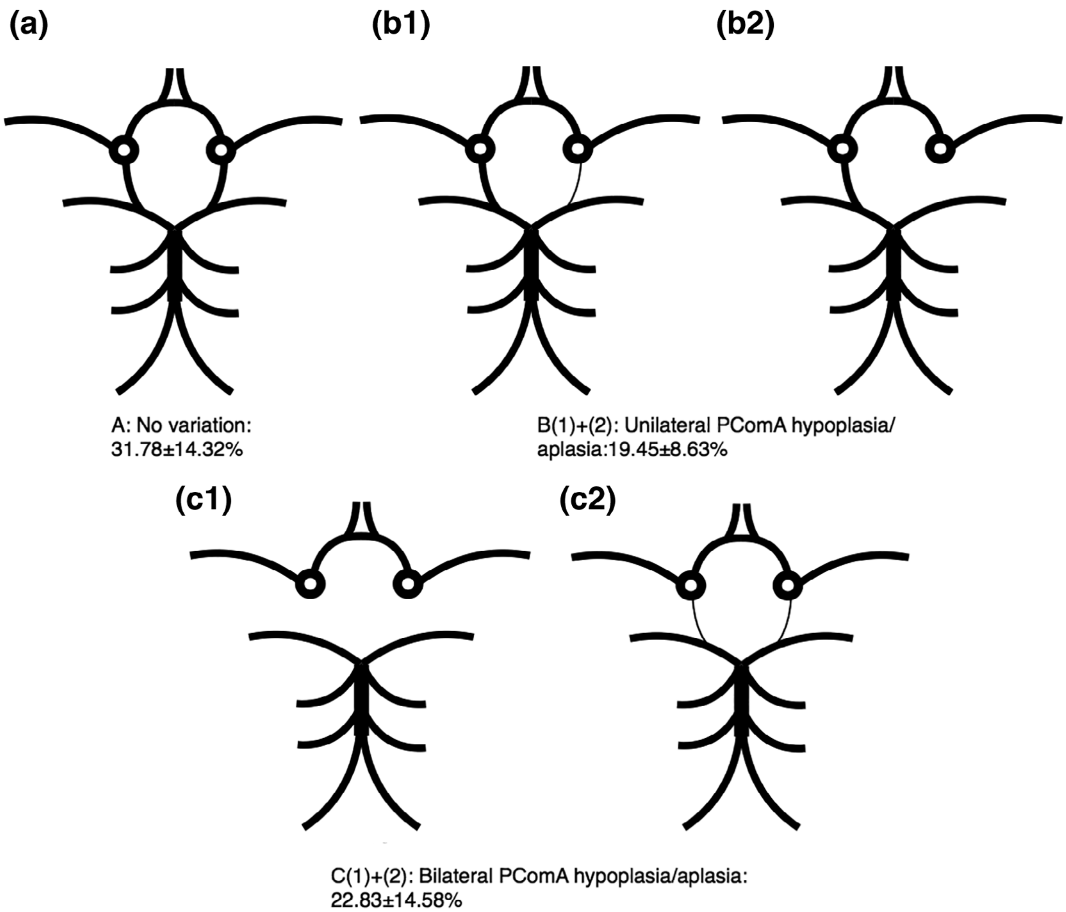

FIGURE 6 Variations of the Circle of Willis examined in this study, and their prevalence following meta-analysis. A: "Normal" CoW, with no variations, present in 31.78 ± 14.32%. B(1): Unilateral PComA hypoplasia, B(2): Unilateral PComA aplasia. Together, the prevalence of B(1) and B (2) was 19.45 ± 8.63%. C(1): Bilateral PComA aplasia, C(2): Bilateral PComA hypoplasia. Together, the prevalence of C(1) and C(2) was 22.83 ± 14.58%. Note how C(1) and C(2) may completely sever communication between the anterior and posterior halves of the CoW

4 | DISCUSSION

4.1 | Prevalence of general variation of the CoW

It is clear from the literature that variations of the CoW are very common (68.22% ± 14.32). For clinicians treating ischemic attacks, strokes, and aneurysms, understanding potential variations is crucial. For example, clinicians treating aneurysms need to be aware that the anatomy is highly likely to exhibit some variation from Willis' originally described circle.

Standard anatomy textbooks often acknowledge that the CoW is highly variable (Moore et al., 2014; Standring & Gray, 2016), noting that there is some variation in approximately 50% of the population (DeSilva et al., 2011). Here, a meta-analysis of the highest quality studies, following screening and critical appraisal, has been performed, and other well-reputed studies (Fisher, 1965; Lazorthes et al., 1979; Riggs, 1963) have been considered whilst reviewing the literature. Whilst the range of reported prevalence of general variation found is wide (42%–92%), descriptive statistics suggest that the average mean prevalence of a variant CoW is 68.22% ± 14.32, in a healthy population.

The results of this review, therefore, find variation is likely to be present in well over half of the general population. The modal reported prevalence 71–80% (30.8% studies) (Figure 3) and 53.84% (n = 14) of the studies analyzed suggest a prevalence of 68.22% or above, and this increases the confidence that the prevalence of a variant CoW is likely to be much higher than currently thought (~70%). Figure 6 displays illustrations of the variations examined in this meta-analysis.

With this in mind, it should be strongly emphasized in standard textbooks and anatomical teaching that Willis' original circle is somewhat unlikely to be encountered. For clinicians commonly performing procedures on the CoW, or for anatomists examining it, an awareness of this is essential to help them prepare to encounter unusual or unfamiliar anatomy.

4.2 | Prevalence of variation of the PComA

Despite the wide range of reported prevalence of general variation, most authors agree the PComA is the vessel most likely to display variation. In the final analysis, 96.88% of studies (Table 2) reported PComA as the most frequently anomalous vessel. This meta-analysis suggests that PComA hypoplasia/aplasia is present unilaterally in 19.45% ± 8.63, and bilaterally in 22.83% ± 14.58 of the population.

Clinically, PComA hypoplasia and aplasia are very significant. The PComA is essential for connecting the anterior and posterior halves of the CoW. A non-patent or non-existent PComA may compromise the ability of the CoW to provide collateral circulation. In this study, bilateral hypoplasia/aplasia was shown to be more common than unilateral, although there was a much wider range of reported prevalence (Figure 5). Clinically, however, this variation is particularly significant: the two halves of the CoW could be anatomically and functionally isolated from each other with no communication between the internal carotid system and vertebrobasilar system. This is illustrated particularly in Figure Six (images C1 and C2). In a condition such as internal carotid artery stenosis, cerebral circulation may rely on collateral blood supply from the vertebrobasilar system. Without a functioning PComA, it is possible that the route for collateral circulation may be compromised, and could contribute to ischemic pathology. (Karatas et al., 2016; Saikia, Handique, Phukan, Lynser, & Sarma, 2014). Whilst some individuals could potentially develop other collateral circulation in the case of a non-functioning PComA, this is highly variable among individuals, and the ability to develop collaterals in pathological conditions (such as ischemic stroke) is not uniform.

Having repeated the literature search at the time of publication, a further relevant cadaveric study, meeting inclusion criteria was found (Cilliers, Vorster, & Page, 2018). This study reported that in 39 cadavers, a variant circle (defined as different to Lazorthes' type 1) (Lazorthes et al., 1979) was present in 59% specimens. Unilateral PComA hypoplasia was present in 23.1% and bilateral hypoplasia in 10.3%. Cilliers et al.'s (2018) results are in tandem with the other studies examined in this analysis and aligned with the statistical results (Figures 3 and 4).

4.3 | Clinical applications of variations of the CoW, particularly the PComA

Being familiar with the most common CoW variations and their prevalence can be of vital importance to clinicians. Many authors have suggested an increased risk of ischemic stroke in the presence of CoW variations (Chuang, Liu, Pan, & Lin, 2008; Hoksbergen et al., 2003; Mukherjee, Jani, Narvid, & Shadden, 2018). Chuang et al. (2008), for example, highlight that hypoplasia of the PComA is associated with an increased risk of infarction, particularly in the thalamic region. Understanding the anatomy of common variations and their prevalence can help us predict the likelihood of patients suffering a stroke, and which regions are likely to be affected. In the absence of traditional risk factors for stroke, such as ICA stenosis, it would be feasible to consider whether an anatomical variation is the CoW is the causative factor.

Mukherjee et al. (2018) suggest that variant CoW anatomy can have an impact on the trajectory of microemboli, and hence lead to infarctions in distal, more unusual areas of the brain. Therefore, being aware of variations and their frequency can help us understand atypical stroke patterns, and predict their likelihood. If a specific variation, of which the prevalence is known, was associated with a particular stroke pattern, it would be possible to predict the likelihood of this stroke pattern occurring.

For neurosurgeons managing aneurysms, being aware of the potential variations in anatomy is essential. Additionally, being aware of their prevalence may also be of crucial importance. Considering, for instance, the prevalence of PComA hypoplasia of approximately 19.45% unilaterally and 22.83% bilaterally, if an aneurysm treatment modality involved vessel sacrifice of one of the PComAs, or relied on one or both of the PComAs to provide collateral circulation throughout the procedure, knowing the likelihood of the variant anatomy could be incredibly useful. It would allow a surgeon to assess the risk of a particular approach, and consider the likelihood of the need for an alternative approach, once the patient is undergoing surgery. Having this prior knowledge can assist a surgeon in becoming better prepared for procedures, and more likely to have prepared an alternative approach, in the case of variant anatomy. Furthermore, understanding which variations are common and their prevalence can help inform clinicians as to whether an endovascular or surgical approach is least likely to disturb the blood supply.

4.4 | Large discrepancies in the reported prevalence of CoW variation exists, and wide ranges of results

This analysis produced a very wide range of results in all domains studied (Figures 3–5). As a result, the estimated prevalence showed large *SD*. Differences in methodology and nomenclature are likely to account for the large range of results seen throughout the literature. Four main reasons have been identified for this wide range.

Firstly, studies on the variability of the CoW have been undertaken using heterogeneous methods. Cadaveric studies used a variety of dissection techniques, and LPI studies ranged between using 3D Time-of-Flight MRA (3D-TOF-MRA) and CT Angiography (CTA). As discussed below, no significant difference was found between cadaveric and LPI studies. Furthermore, a variety of sample sizes have been used throughout the research, ranging from 30 to 2,246 (Table 2), and it was not possible to identify an appropriate sample size for exclusion in the present study. Hence, with a variety of methods and sample sizes being used, it is unsurprising that variation exists between studies.

Secondly, nomenclature varies between studies, particularly with regards to the definition of a hypoplastic vessel. Throughout the literature, various definitions have been used (Table 2), with <1 mm the most commonly used (56.25%), particularly in cadaveric studies. Several other studies have used <0.8 mm to define a hypoplastic vessel (15.63%), appearing more frequently in LPI studies. 18.75% of studies analyzed failed to provide any definition for a hypoplastic vessel (Table 2). With differing definitions throughout the literature, it is likely that what one study considered a hypoplastic vessel was not considered hypoplastic by another. If a study was using <0.8 mm as the definition, for example, they will have excluded vessels 0.8–1.0 mm diameter, which others may have considered hypoplastic, and this may have falsely decreased their overall reported prevalence of hypoplasia.

Thirdly, different classification systems have been used to categorize variations, throughout the literature. Lazorthes et al. (1979) describe 22 separate variant CoWs, whilst Krabbe-Hartkamp et al. (1998) describe 10 anterior and 10 posterior CoW variations. Some authors have used or adapted these systems (Table 2) when describing their findings. However, 46.88% of studies in this review did not use any established classification system. With different studies using different or no classification systems, a comparison is difficult and reduces confidence that two studies describe the same variation and are truly comparable.

Finally, population differences in anatomy likely exist. Studies have been performed on five continents, and it is reasonable to expect variation in the frequencies of anatomical variants between populations. Interestingly, PComA hypoplasia/aplasia was reported as particularly high in Chen et al.'s (2004), Li et al.'s (2011) and Qiu et al.'s (2015) studies, all performed in a similar region of Asia (Table 2). Hence, some differences in prevalence are likely to be due to population-specific anatomical variation.

4.5 | Differences between cadaveric and LPI studies

There is no statistically significant difference between the results of cadaveric and LPI studies. On visual examination of the scatter graphs (Figures 3, 4, and 5), the results of different study types overlap, and there is no discernible pattern or correlation between them.

Throughout the literature, authors have suggested cadaveric and LPI studies should not be compared and analyzed together for several reasons (Klimek-Piotrowska et al., 2016; Li et al., 2011). Cadaveric studies examine vessels that have undergone formalin fixation or other preserving methods, during which vessel diameters may change and fail to represent the true dimensions of the vessel (Li et al., 2011; Saikia, Handique, Phukan, Lynser, & Sarma, 2014), as blood is not actively flowing through them, as would be in an LPI study. Thus, cadaveric and LPI studies may give different results. Furthermore, cadaveric studies allow direct visualization of the vessels in situ (Qiu et al., 2015); such access is impossible in CTA or 3D-TOF-MRA studies. Despite this, the results of the present study show that no statistically significant difference exists between the results of the highest quality studies. Hence, for this review, it was considered appropriate to combine the two types of study for descriptive statistics, but the results should be interpreted with a degree of caution.

4.6 | Future directions and recommendations

The outcome of this review is that the prevalence of CoW variation, in general, is 68.22% ± 14.32, (range 53.9%–82.54%) with confidence that it is likely to be considerably over 50%. The results show the most frequently reported prevalence of variation was in the range of 71–80% (n = 8), whilst 88.5% of studies analyzed reported the prevalence of a variant CoW as >51%. However, to produce a more accurate estimate for the prevalence of variations, and to improve understanding of the types of variation and their frequency, a comprehensive classification system needs to be established and adhered to in future studies.

It is, therefore, pertinent that a universally accessible database is created, collating all current, high-quality research. Such a database should be created from an expert consensus, of anatomists who have extensive experience studying the area. The consensus should also involve clinicians, with regular, ongoing experience managing relevant conditions, such as stroke and aneurysms, to ensure the resulting classification is of clinical relevance. This database would include known variations of the CoW, their estimated prevalence, and a clear definition for each. This would also include an agreed definition for hypoplasia, preferably <1 mm, as this has been most widely used throughout the literature analyzed (Table 2). All future research could henceforth refer to this database to describe their results, unifying the reporting and comparison of CoW variations and prevalence. In doing so, the true prevalence of variation will likely be found.

Such a database could also be referred to by clinicians to whom the anatomy is relevant, to familiarize themselves with unusual anatomy, and to increase awareness of new variations and changes in patterns of prevalence.

It is also recommended that when teaching the anatomy of the CoW, in both undergraduate and postgraduate settings, several points should be emphasized. Firstly, it should be highlighted that the CoW commonly displays variability, with considerably over 50% of the population showing some form of variation. Additionally, the areas most commonly exhibiting variation, such as the PComA should be emphasized. Furthermore, the clinical application of these variations, such as their relevance to stroke patterns, embolus distribution, or aneurysm treatment approaches should be highlighted and considered in tandem with anatomical teaching. The depth of discussion of all of these areas should, of course, depend on the audience and their expected knowledge level.

4.7 | Limitations

It was not possible to determine an appropriate cut off value for the sample size of studies. Papers examining smaller sized samples (i.e., <200) may have statistically unreliable results, which may have impacted on the results of the meta-analysis. If more high-quality studies were available, a sample size cut-off may have been established.

The searching, review and appraisal of the studies considered in this review were carried out by a single investigator, raising the potential for observer bias. The critical appraisal grading scheme was assessed by two independent experts (a University Academic and a Consultant Neurosurgeon.)

5 | CONCLUSIONS

The CoW is a network of arteries surrounding the base of the brain, providing collateral circulation to prevent ischemic pathology. Variations from the originally described model of the CoW are common, with the present study estimating variant CoWs to be present in 68.22% ± 14.32%. Variations are most commonly seen in the PComA, with unilateral and bilateral hypoplasia or aplasia present in 19.45% ± 8.63% and 22.83 ± 14.58% of the neurologically healthy population respectively.

To provide more accurate and precise estimates for the prevalence of variations, it is suggested that a universal classification system of known variations is created and used in all future studies of CoW anatomy. Within this classification system, an agreed definition of a hypoplastic vessel should be established; for instance, <1 mm. Understanding the prevalence of variations and how they can impact pathology may help lead to more effective prevention and treatment of such conditions.

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REFERENCES

Al-Hussain, S. M., Shoter, A. M., & Bataina, Z. M. (2001). Circle of Willis in adults. *Saudi Medical Journal*, *22*, 895–898.

Alpers, B. J. (1963). Circle of Willis in cerebral vascular disorders. *Archives of Neurology*, *8*, 398.

Ardakani, S. K., Dadmehr, M., Nejat, F., Ansari, S., Eftekhar, B., Tajik, P., … Abdi-Rad, A. (2008). The cerebral arterial circle (circulus arteriosus cerebri): An anatomical study in fetus and infant samples. *Pediatric Neurosurgery*, *44*, 388–392.

Battacharji, S., & Hutchinson, E. (1967). The circle of Willis: The incidence of developmental abnormalities in normal and infracted brains. *Brain*, *90*, 747–758.

Chen, H. W., Yen, P. S., Lee, C. C., Chen, C. C., Chang, P. Y., Lee, S. K., … Bin, C. A. S. (2004). Magnetic resonance angiographic evaluation of circle of Willis in general population: A morphologic study in 507 cases. *Chinese Journal of Radiology*, *29*, 223–229.

Chuang, Y. M., Liu, C. Y., Pan, P. J., & Lin, C. P. (2008). Posterior communicating artery hypoplasia as a risk factor for acute ischemic stroke in the absence of carotid artery occlusion. *Journal of Clinical Neuroscience*, *15*, 1376–1381.

Cilliers, K., Vorster, W., & Page, B. J. (2018). The anatomical variation of the circulus arteriosus cerebri in a cadaver cohort representing the population dynamics of the Western cape. *British Journal of Neurosurgery*, *32*, 61–67.

Critical-Appraisal-Skills-Programme. (2017a). CASP (Case Control). CASP Website. http://www.casp-uk.net/checklists (accessed Aug 2017).

Critical-Appraisal-Skills-Programme. (2017b). CASP (Cohort). CASP Website. http://www.casp-uk.net/checklists (accessed Aug 2017).

DeSilva, K. R. D., Silva, R., Amaratunga, D., Gunasekera, W. S. L., & Jayesekera, R. W. (2011). Types of the cerebral arterial circle (circle of Willis) in a Sri Lankan population. *BMC Neurology*, *11*, 5.

DeSilva, K. R. D., Silva, R., Gunasekera, W. S. L., & Jayesekera, R. W. (2009). Prevalence of typical circle of Willis and the variation in the anterior communicating artery: A study of a Sri Lankan population. *Annals of Indian Academy of Neurology*, *12*, 157–161.

Eftekhar, B., Dadmehr, M., Ansari, S., Ghodsi, M., Nazparvar, B., & Ketabchi, E. (2006). Are the distributions of variations of circle of Willis different in different populations? – Results of an anatomical study and review of literature. *BMC Neurology*, *6*, 22.

El-Barhoun, E. N., Gledhill, S. R., & Pitman, A. G. (2009). Circle of Willis artery diameters on MR angiography: An Australian reference database. *Journal of Medical Imaging and Radiation Oncology*, *53*, 248–260.

Federative Committee on Anatomical Terminology. (1998). Terminologia Anatomica. Stuttgart, Germany: Thieme.

Fisher, C. M. (1965). The circle of Willis: Anatomical variations. *Vascular Diseases*, *2*, 99–105.

Gunnal SA, Farooqui MS, Wabale RN. (2014). Anatomical variations of the circulus arteriosus in cadaveric human brains. *Neurology Research International*. *2014*:1:687281 (Online).

Hashemi, S., Mahmoodi, R., & Abbas, A. (2013). Variations in the anatomy of the Willis' circle: A 3-year cross-sectional study from Iran (2006-2009). Are the distributions of variations of circle of Willis different in different populations? Result of an anatomical study and review of literature. *Surgical Neurology International*, *4*, 65.

Henry, B. M., Roy, J., Ramakrishnan, P. K., Vikse, J., Tomaszewski, K. A., & Walocha, J. A. (2015). Association of migraine headaches with anatomical variations of the circle of Willis: Evidence from a meta-analysis. *Neurologia i Neurochirurgia Polska*, *49*, 272–277.

Hoksbergen, A. W. J., Legemate, D. A., Csiba, L., Csati, G., Siro, P., & Fulesdi, B. (2003). Absent collateral function of the circle of Willis as risk factor for ischemic stroke. *Cerebrovascular Diseases*, *16*, 191–198.

Idowu, O. E., Malomo, A. O., & Akang, E. U. (2010). Surgical anatomy of the vertebrobasilar territory and posterior circle of Willis. *West African Journal of Medicine*, *29*, 230–234.

Kapoor, K., Singh, B., & Dewan, L. I. J. (2008). Variations in the configuration of the circle of Willis. *Anatomical Science International*, *83*, 96–106.

Karatas, A., Coban, G., Cinar, C., Oran, I., & Uz, A. (2015). Assessment of the circle of Willis with cranial tomography angiography. *Medical Science Monitor*, *21*, 2647–2652.

Karatas, A., Yilmaz, H., Coban, G., Koker, M., & Uz, A. (2016). The anatomy of circulus arteriosus cerebri (circle of Willis): A study in Turkish population. *Turkish Neurosurgery*, *26*, 54–61.

Kayembe, K. N., Sasahara, M., & Hazama, F. (1984). Cerebral aneurysms and variations in the circle of Willis. *Stroke*, *15*, 846–850.

Klimek-Piotrowska, W., Kopeć, M., Kochana, M., Krzyżewski, R. M., Tomaszewski, K. A., Brzegowy, P., & Walocha, J. (2013). Configurations of the circle of Willis: A computed tomography angiography based study on a polish population. *Folia Morphologica*, *72*, 293–299.

Klimek-Piotrowska, W., Rybicka, M., Wojnarska, A., Wójtowicz, A., Koziej, M., & Hołda, M. K. (2016). A multitude of variations in the configuration of the circle of Willis: An autopsy study. *Anatomical Science International*, *91*, 325–333.

Krabbe-Hartkamp, M. J., van der, G. J., de, L. F. E., de, G. J. C., Algra, A., Hillen, B., … Mali, W. P. (1998). Circle of Willis: Morphologic variation on three-dimensional time-of-flight MR angiograms. *Radiology*, *207*, 103–111.

Lazorthes, G., Santini, J., & Salamon, G. (1979). The arterial circle of the brain (Circulus Arteriosus Cerebri). *Anatomia Clinica*, *257*, 241–257.

Li, Q., Li, J., Lv, F., Li, K., Luo, T., & Xie, P. (2011). A multidetector CT angiography study of variations in the circle of Willis in a Chinese population. *Journal of Clinical Neuroscience*, *18*, 379–383.

Macchi, C., Lova, R. M., Miniati, B., Gulisano, M., Pratesi, C., Conti, A. A., & Gensini, G. F. (2002). The circle of Willis in healthy older persons. *The Journal of Cardiovascular Surgery*, *43*, 887–890.

Malamateniou, C., Adams, M. E., Srinivasan, L., Allsop, J. M., Counsell, S. J., Cowan, F. M., … Rutherford, M. A. (2009). The anatomic variations of the circle of Willis in preterm-at-term and term-born infants: An MR angiography study at 3T. *American Journal of Neuroradiology*, *30*, 1955–1962.

Moore, K., Dalley, A., & Agur, A. (2014). *Clinically orientated anatomy* (7th ed.). Baltimore, MD, Philadelphia, PA: Wolters Kluwer.

Mukherjee, D., Jani, N. D., Narvid, J., & Shadden, S. C. (2018). The role of circle of Willis anatomy variations in cardio-embolic stroke: A patient-specific simulation based study. *Annals of Biomedical Engineering*, *46*(8), 1128–1145.

Naveen, S., Bhat, V., & Karthik, G. (2015). Magnetic resonance angiographic evaluation of circle of Willis: A morphologic study in a tertiary hospital set up. *Annals of Indian Academy of Neurology*, *18*(4), 391–397.

Nowinski, W. L., Thirunavuukarasuu, A., Volkau, I., Marchenko, Y., Aminah, B., Puspitasari, F., & Runge, V. M. (2009). A three-dimensional interactive atlas of cerebral arterial variants. *Neuroinformatics*, *7*, 255–264.

Papantchev, V., Hristov, S., Todorova, D., Naydenov, E., Paloff, A., Nikolov, D., … Ovtscharoff, W. (2007). Some variations of the circle of Willis, important for cerebral protection in aortic surgery—A study in eastern Europeans. *European Journal of Cardio-Thoracic Surgery*, *31*, 982–989.

Papantchev, V., Stoinova, V., Aleksandrov, A., Todorova-Papantcheva, D., Hristov, S., Petkov, D., … Ovtscharoff, W. (2013). The role of Willis circle variations during unilateral selective cerebral perfusion: A study of 500 circles. *European Journal of Cardio-Thoracic Surgery*, *44*, 743–753.

Qiu, C., Zhang, Y., Xue, C., Jiang, S., & Zhang, W. (2015). MRA study on variation of the circle of Willis in healthy Chinese male adults. *BioMed Research International*, *2015*, 976340 (Online).

van-Raamt, A. F., Mali, V. P., van-Laar, P. J., & van der Graff, Y. (2006). The fetal variant of the circle of Willis and its influence on the cerebral collateral circulation. *Cerebrovascular Diseases*, *22*, 217–224.

Riggs, H. E. (1963). Variation in form of circle of Willis. *Archives of Neurology*, *8*(8), 8.

Saha, A., Sarkar, A., & Mandal, S. (2015). A cadaveric study of bilateral configuration of posterior bifurcation of posterior communicating artery in Indian population. *Journal of Clinical and Diagnostic Research*, *9*(3), AC1–AC4.

Saikia, B., Handique, A., Phukan, P., Lynser, D., & Jamil, M. (2014). Study of anomalies in the circle of Willis using magnetic resonance angiography in north eastern India. *Journal of the Anatomical Society of India*, *63*, 67–73.

Saikia, B., Handique, A., Phukan, P., Lynser, D., & Sarma, A. (2014). Circle of Willis: Variant forms and their embryology using gross dissection and magnetic resonance angiography. *International Journal of Anatomy and Research*, *2*, 344–353.

Siddiqi, H., Tahir, M., & Lone, K. P. (2013). Variations in cerebral arterial circle of Willis in adult Pakistani population. *Journal of College of Physicians and Surgeons Pakistan*, *23*, 615–619.

Standring, S., & Gray, H. (2016). *Gray's anatomy: The anatomical basis of clinical practice* (41st ed.). Philadephia, PA: Elsevier.

Voljevica, A., & Kapur, E. (2005). Angiographic analysis of variations of the posterior segment of the circle of Willis. *Bosnian Journal of Basic Medical Sciences*, *5*, 30–34.

Willis, T. (1664). *Cerebri Anatome: Cui Accessit Nervorum Descriptio et Usus*. London: Oxford Publishing House.

Yeniçeri, I. Ö., Çullu, N., Deveer, M., & Yeniçeri, E. N. (2017). Circle of Willis variations and artery diameter measurements in the Turkish population. *Folia Morphologica*, *76*, 420–425.

Zhou, H., Sun, J., Ji, X., Lin, J., Tang, S., Zeng, J., & Fan, Y. (2016). Correlation between the integrity of the circle of Willis and the severity of initial noncardiac cerebral infarction and clinical prognosis. *Medicine*, *95* (10), 1–7.

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