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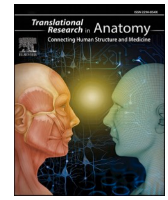

Review

Occipitalization of the atlas: prevalence, functional and anatomical considerations. A systematic review and meta-analysis

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ABSTRACT

Background: Occipitalization of the atlas, defined as a congenital fusion between the first cervical vertebra (C1) and the occipital bone, is an uncommon anatomical variant of the craniovertebral junction. Reported prevalence in the general population varies widely, and the condition is often identified incidentally during imaging or anatomical assessment.

Objective: To synthesize available evidence on the prevalence of atlas occipitalization and to describe its anatomical characteristics across different populations and study designs.

Methods: A comprehensive literature search was conducted in MEDLINE, Scopus, Web of Science, Google Scholar, CINAHL, and LILACS from inception to January 2025. Study selection and data extraction were performed independently by four reviewers. Methodological quality was assessed using the Anatomical Quality Assessment (AQUA) tool. A random-effects meta-analysis was applied to estimate pooled prevalence values and explore predefined subgroups.

Results: Twenty-five studies met the inclusion criteria for qualitative synthesis, of which eleven were included in the meta-analysis, encompassing a total of 4219 subjects. The pooled prevalence of atlas occipitalization was 0.64 % (95 % confidence interval: 0.00–1.00 %). Variability in prevalence estimates was observed across populations and assessment methods.

Conclusion: Atlas occipitalization is a rare congenital anatomical variant of the craniovertebral junction. Although often asymptomatic, its identification is anatomically relevant due to potential associations with other craniovertebral anomalies. Awareness of this variant is important for accurate anatomical interpretation and for planning procedures involving the craniovertebral junction.

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1. Introduction

The atlas (C1), the first cervical vertebra, is anatomically distinct from the remaining vertebrae due to the absence of a vertebral body and spinous process. Instead, it consists of two lateral masses connected by anterior and posterior arches, whose superior articular facets articulate with the occipital condyles to form the atlanto-occipital joint, a key component of the craniovertebral junction responsible primarily for flexion and extension of the head [1,2]. The atlanto-occipital joint is classified as a synovial condyloid joint and is stabilized by an articular capsule and surrounding ligamentous structures, including the anterior atlanto-occipital ligament and the posterior atlanto-occipital membrane. Notably, no intervertebral disc is present between the occiput and C1, and the articular surfaces are covered by hyaline cartilage, allowing a balance between mobility and stability at the craniocervical junction (Figs. 1 and 2) [3].

Under normal developmental conditions, the atlas remains anatomically independent. However, disruptions in segmentation or ossification during embryogenesis derived from the first cervical sclerotome may result in congenital fusion of the atlas with the occipital bone or, less frequently, with the axis (C2) [4–6]. These segmentation failures represent a spectrum of craniovertebral anomalies with potential anatomical and biomechanical relevance. Occipitalization of the atlas refers to a congenital condition characterized by partial or complete fusion of C1 to the occipital bone. This fusion may be osseous or fibrous and can involve the anterior arch, posterior arch, lateral masses, or a combination of these structures, resulting in considerable morphological variability [7–9]. Although frequently asymptomatic and detected incidentally on imaging studies, atlas occipitalization has been associated with alterations in craniovertebral morphology and cervical biomechanics, particularly when coexisting with other craniovertebral anomalies such as basilar invagination or Chiari malformation [10].

Given the anatomical variability and inconsistent reporting across studies, the true prevalence of atlas occipitalization remains unclear. Therefore, the aim of this systematic review and meta-analysis is to synthesize the available evidence on the prevalence of atlas occipitalization across different populations and study designs, while providing an anatomical framework for understanding this congenital craniovertebral variant.

2. Methods

2.1. Protocol and registration

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [11]. The review protocol was prospectively registered in the Systematic Reviews Registry (registration number: to be added upon acceptance/available upon request).

2.2. Electronic search strategy

A comprehensive electronic search was performed in January 2025 across the following databases: MEDLINE (via PubMed), Web of Science (WOS), Scopus, Google Scholar, CINAH, and Latin American and Caribbean Literature in Health Sciences (LILACS). The search covered all records from database inception through January 2025.

The search strategy combined controlled vocabulary (MeSH terms, when available) and free-text terms related to atlas occipitalization and anatomical variation. The primary search terms included: *"Atlas bone"*, *"Occipital bone"* (MeSH), *"Atlanto-occipital joint"*, *"Occipitalization of the atlas"*, *"Atlas fusion"*, *"Craniovertebral junction"*, *"Congenital anomalies"*, *"Clinical anatomy"* (MeSH), and *"Anatomical variations"*. Boolean operators (AND, OR, NOT) were applied to refine the search strategy. A detailed search syntax for each database is provided in Supplementary Table 1. Additionally, the reference lists of eligible articles were manually screened to identify potentially relevant studies not captured by the electronic search.

2.3. Eligibility criteria

This systematic review included studies that evaluated occipitalization of the atlas and its anatomical, radiological, or clinical associations at the craniovertebral junction. Inclusion criteria were as follows: 1).

Fig. 1. Oblique view of the base of the skull of a 55-year-old male with an occipitalized atlas (circled).

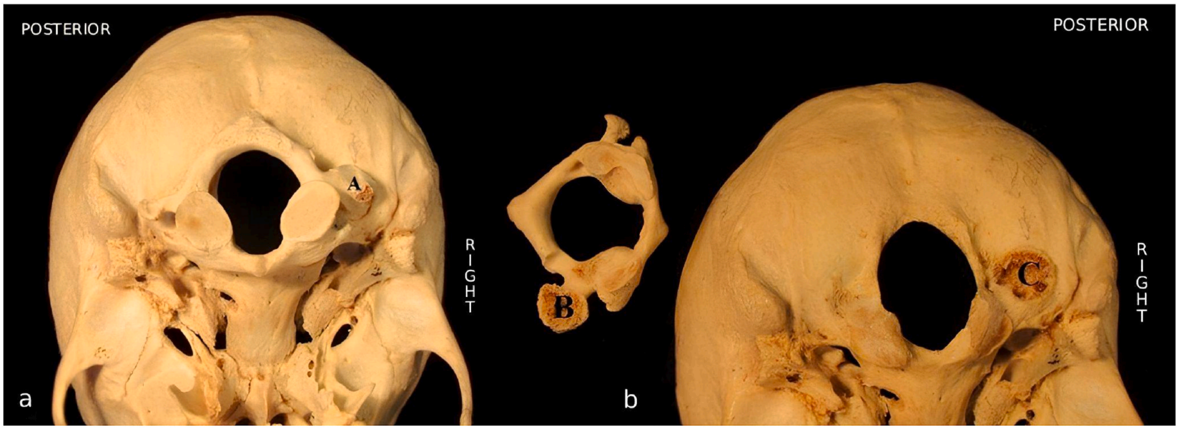

Fig. 2. Occipitalization of the atlas. (a) Inferior view of a 32-year-old female showing the site of fusion (Label A).(b) Inferior view showing the site of fusion on the superior aspect of the atlas transverse process (Label B) and the bony plaque of the occipitalized atlas (Label C).

Studies based on human cadaveric dissections or imaging techniques (e.g., CT, MRI, radiography) identifying occipitalization of the atlas. 2). Studies reporting prevalence data and/or describing morphological variants of atlas occipitalization. 3). Studies examining clinical correlations, including neurological, musculoskeletal, or vascular implications involving the head and neck region. 4). Original research articles (retrospective or prospective observational studies) published in English in peer-reviewed journals.

Exclusion criteria were: 1). Studies conducted in animal models. 2). Studies focused on other cranial or cervical anatomical variants not involving atlas occipitalization. 3). Case reports, review articles, letters to the editor, editorials, conference abstracts, and expert opinions.

2.4. Study selection

Three authors independently conducted the study selection process. Initially, two reviewers (Valenzuela JJ and Orellana M) screened the titles and abstracts of all retrieved records. Full-text articles were subsequently obtained for studies considered potentially eligible. In cases of disagreement, a third reviewer (Sanchis- J) was consulted to achieve consensus. Inter-reviewer reliability was assessed using Cohen's kappa statistic, yielding a kappa value of 0.72, which indicates good agreement among reviewers.

2.5. Data collection process

Data extraction was independently performed by two authors (Nova P and Orellana m) using a standardized data extraction form. The following variables were collected from each included study: a) Author (s) and year of publication, b) Sample size and study design, c) Age and sex distribution of participants, d) Type of occipitalization variant and reported prevalence, e) Geographic region of the study population, f) Associated clinical signs and symptoms, g) Relevant anatomical and clinical considerations. Discrepancies in data extraction were resolved through discussion until consensus was reached.

2.6. Methodological quality assessment

The methodological quality and risk of bias of the included studies were assessed using the Anatomical Quality Assessment (AQUA) tool, developed by the International Working Group on Evidence-Based Anatomy (IEBA) [12]. Two reviewers (Valenzuela JJ and Nova P) independently evaluated the five AQUA domains. Any disagreements were resolved by consensus. Results of the quality assessment were summarized in both tabular and graphical formats. To assess publication bias and heterogeneity, funnel plot analyses were performed, examining the relationship between effect size and study precision across the included studies.

2.7. Statistical methods

Quantitative data extracted from the eligible studies were synthesized using RStudio software (R Foundation for Statistical Computing, Vienna, Austria), accessed in June 2025. A meta-analysis was conducted to estimate the pooled prevalence of atlas occipitalization across the included studies.

Prevalence proportions were stabilized using the Freeman Tukey double arcsine transformation, and pooled estimates were calculated employing the DerSimonian and Laird random-effects model. A random-effects approach was selected a priori due to the expected clinical, anatomical, and methodological heterogeneity among studies, including differences in population characteristics, imaging modalities, and classification criteria. Statistical heterogeneity was assessed using Cochran's Q (chi-square) test and quantified with the I^2 statistic. The magnitude of heterogeneity was interpreted based on I^2 values as follows: 0–40 % (low or no heterogeneity), 30–60 % (moderate heterogeneity), 50–90 % (substantial heterogeneity), and 75–100 % (considerable heterogeneity), with corresponding 95 % confidence intervals (CI) reported [8].

Subgroup analyses were performed when sufficient data were available to explore potential sources of heterogeneity, including study design, geographic region, and method of anatomical assessment. Meta-analytic results were visually presented using forest plots, and potential publication bias was evaluated through funnel plot inspection.

3. Results

3.1. Selection of articles

The electronic database search identified 1378 records matching the predefined search strategy. After removal of duplicates, titles and abstracts were screened for relevance. Following this initial screening, 46 articles were selected for full-text evaluation. After application of the eligibility criteria, 25 studies met the inclusion criteria and were incorporated into the qualitative synthesis. Of these, 11 studies provided sufficient quantitative data and methodological homogeneity to be included in the meta-analysis.

The included studies were characterized by clearly defined samples, explicit reporting of prevalence estimates, and transparent methodological approaches. The study selection process is summarized in a PRISMA 2020 flow diagram (Fig. 3).

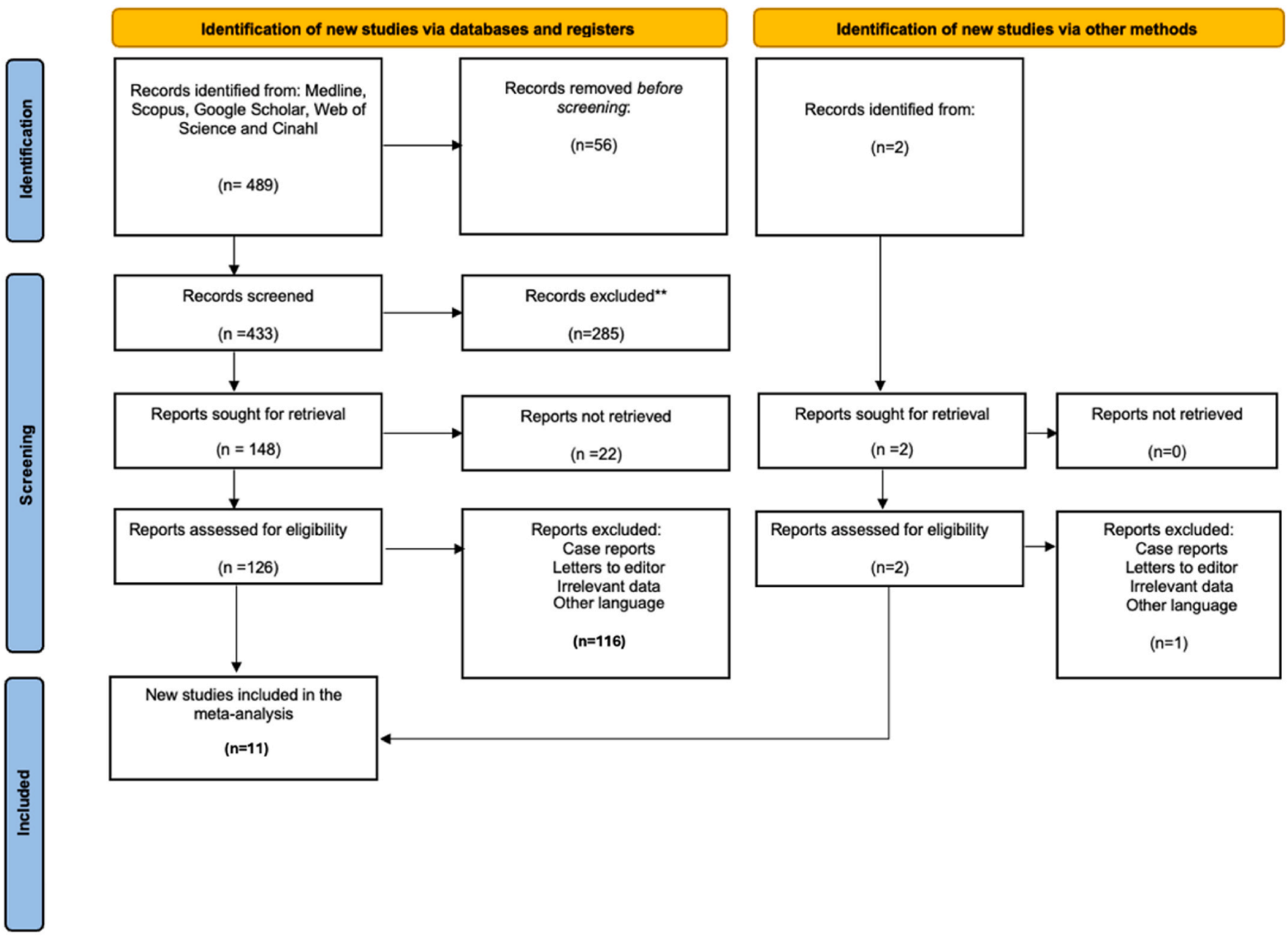

Fig. 3. PRISMA 2020 flow diagram of the study selection process.

3.2. Characteristics of included studies

A total of 11 studies met the criteria for inclusion in the quantitative synthesis (meta-analysis), comprising a cumulative sample of 4219 subjects [13–23]. The included studies varied with respect to study design, population characteristics, geographic distribution, and methods used to identify atlas occipitalization, including cadaveric dissection and radiological assessment. The main characteristics of the included studies are summarized in Table 1.

3.3. Prevalence of atlas occipitalization and subgroup analyses

Six forest plots of proportions were generated to estimate the overall prevalence of atlas occipitalization and to explore differences across predefined subgroups, including geographic region, sex, and diagnostic methodology.

3.3.1. Overall prevalence

Among these, **11 studies** met the criteria for inclusion in the quantitative synthesis [13–23]. The pooled prevalence was 0.64 % (95 % confidence interval [CI]: 0.00–1.00 %), as illustrated in Fig. 4 (Overall prevalence of atlas occipitalization).

Individual study estimates demonstrated low dispersion with largely overlapping confidence intervals. Statistical heterogeneity was moderate ($I^2 = 47.4$ %), indicating that less than half of the observed variance was attributable to between-study heterogeneity. These findings support

Table 1
Characteristics of included studies on atlas occipitalization.

Author (Year)	Geographic region	Age/sex	Cases/total	Prevalence (%)	Method of analysis
Harrower (1923) [13]	Singapore	Not reported	6/800	0.75	Dry skull
Al-Motabagani (2006) [14]	Saudi Arabia	Age 40–45 years; male	1/109	0.92	Dry skull
Iisuka (2008) [15]	Japan	Mean age 59.3 years; 8 males/18 females	5/26	19.23	Radiography and CT
Miyata (2009) [16]	Japan	Adults; 9 males/20 females	3/29	10.34	Radiography and CT
Saini (2009) [17]	India	Adults; 1 male/1 female	2/126	1.59	Dry skull
Ataka (2010) [18]	Japan	Age 63–75 years; females (n = 8)	1/8	12.50	Radiography, MRI
Jadhav (2012) [19]	India	Adults; sex not reported	1/150	0.67	Dry skull
Mudaliar (2013) [20]	India	Not reported	2/200	1.00	Dry skull
Khamanarong (2013) [21]	Thailand	Age 25–92 years; 373 males/260 females	2/633	0.32	Dry skull
Kim (2015) [22]	South Korea	Mean age 49.0 years; 639 males/390 females	1/1029	0.10	Cervical 3D CT
Boekkooi (2024) [23]	South Africa	Mean age 48.7 years; 766 males/353 females	3/1119	0.27	Dry skull

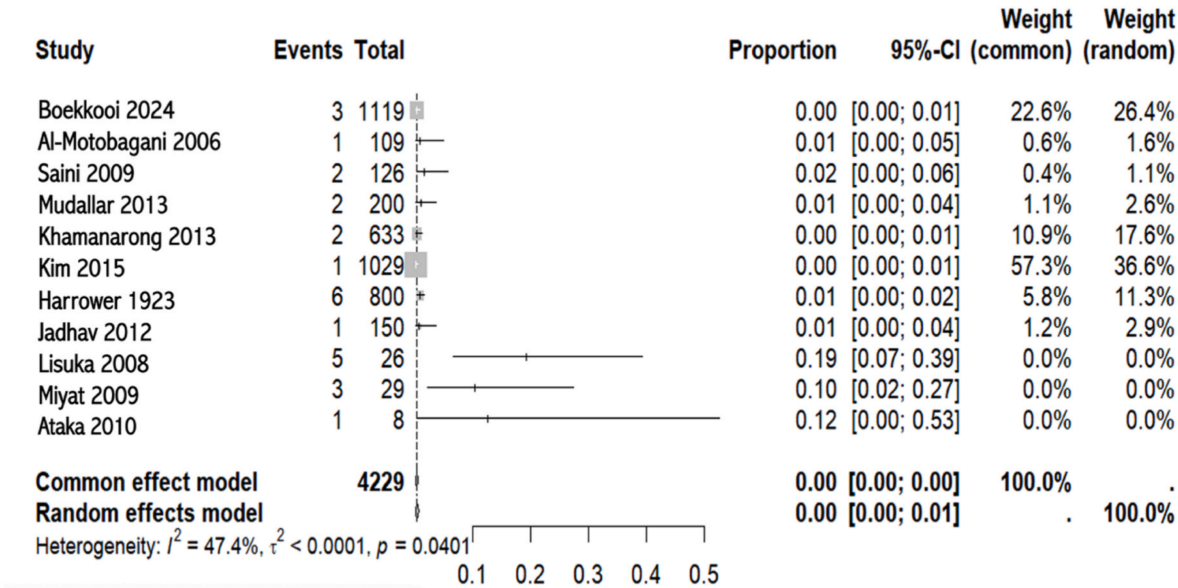

Fig. 4. Forest plot of the prevalence of atlas occipitalization (overall analysis).

the robustness of the pooled prevalence estimate and justify the use of a random-effects model.

3.3.2. Geographic subgroup: Asian population

A subgroup meta-analysis focusing on studies conducted in Asia included 10 eligible studies [13–22]. The pooled prevalence of atlas occipitalization in Asian populations was 0.77 % (95 % CI: 0.00–1.00 %), as shown in Fig. 5 (Prevalence in Asian populations).

Moderate heterogeneity was observed ($I^2 = 52.5$ %), suggesting the influence of population-specific or methodological factors. Despite this variability, the prevalence estimates were generally consistent across studies, with larger samples contributing greater statistical weight.

3.3.3. Sex-based subgroup: female subjects

Five studies reporting sex-specific data in female subjects were included in this subgroup analysis [15–18,23]. The pooled prevalence of atlas occipitalization among women was 1.0 % (95 % CI: 0.04–1.00 %), as depicted in Fig. 6 (Prevalence in female subjects). Heterogeneity was low to moderate ($I^2 = 37.2$ %), and confidence intervals largely overlapped. The Doi plot demonstrated symmetry, indicating a low risk of publication bias. These findings suggest a stable prevalence estimate in female populations.

3.3.4. Sex-based subgroup: male subjects

Seven studies reporting prevalence in male subjects were included [14–18,21,23]. The pooled prevalence of atlas occipitalization in men was 0.44 % (95 % CI: 0.00–1.00 %), as shown in Fig. 7 (Prevalence in male subjects). Statistical heterogeneity was negligible ($I^2 = 0.4$ %), indicating high consistency across studies. The forest plot demonstrates uniform contributions of individual studies, supporting the reliability of the pooled estimate for this subgroup.

3.3.5. Diagnostic method subgroup: cadaveric studies

Seven cadaveric studies were included in this subgroup analysis [13, 14,19–21,23]. The pooled prevalence of atlas occipitalization was 0.00 % (95 % CI: 0.00–1.00 %), as illustrated in Fig. 8 (Prevalence in

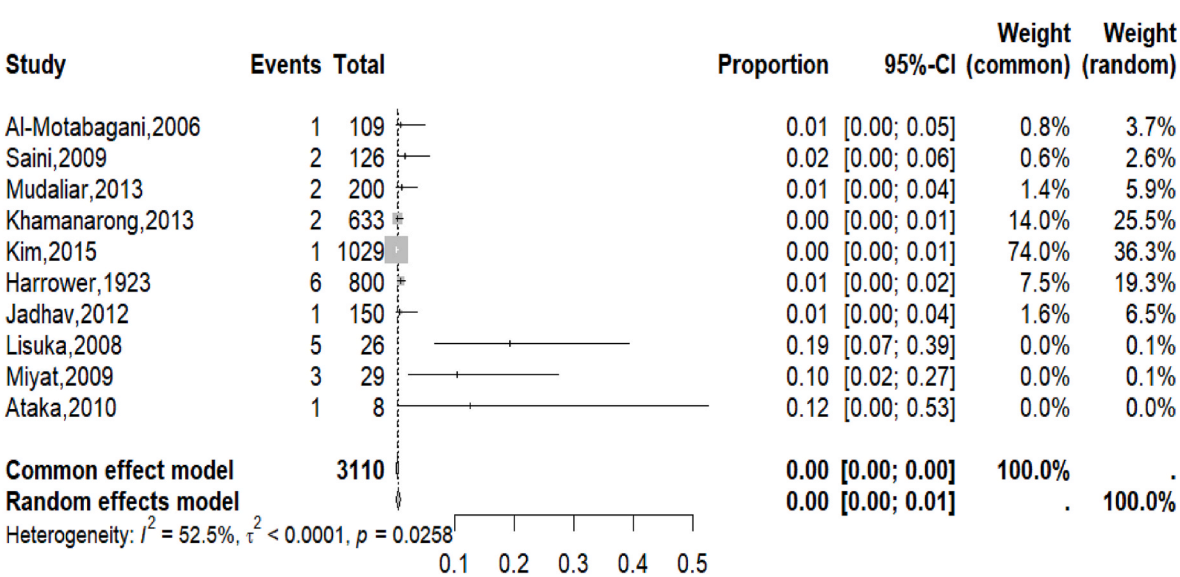

Fig. 5. Forest plot of the prevalence of atlas occipitalization in Asian populations.

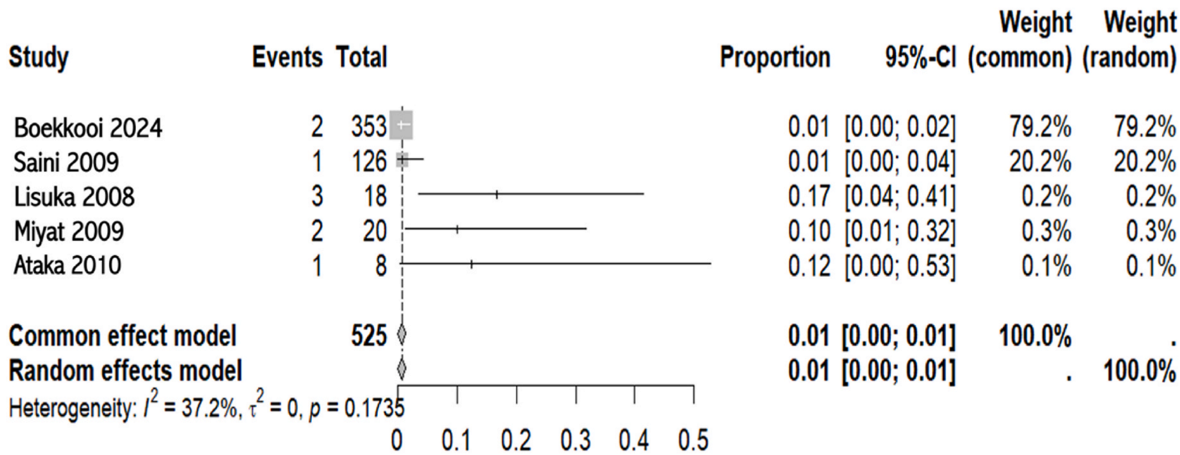

Fig. 6. Forest plot of the prevalence of atlas occipitalization in female subjects.

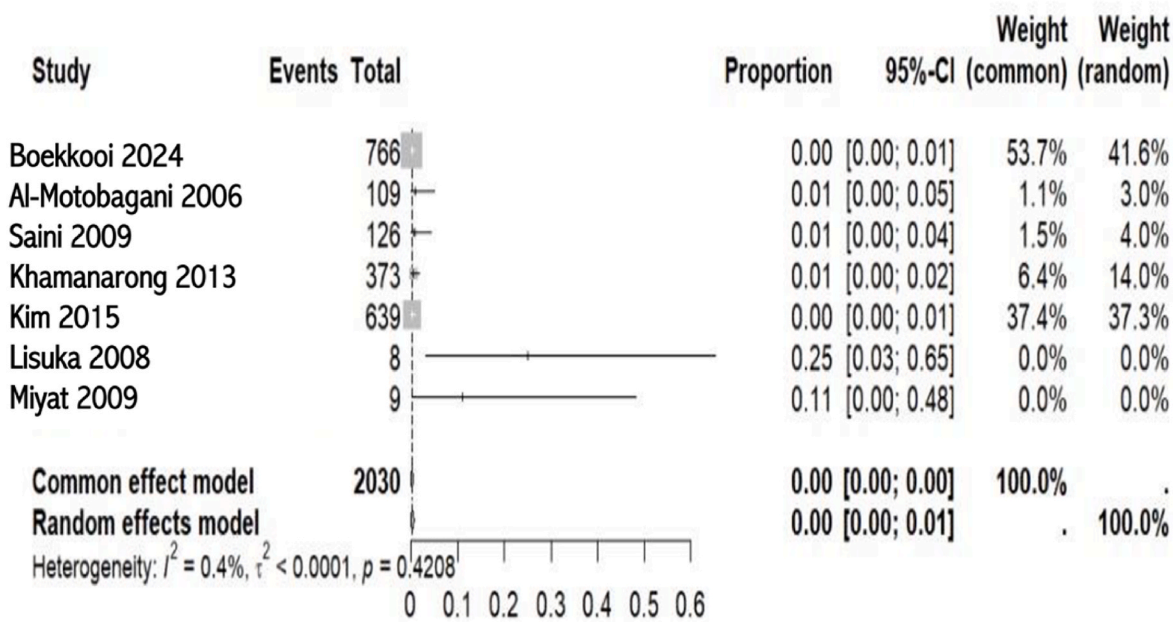

Fig. 7. Forest plot of the prevalence of atlas occipitalization in male subjects.

cadaveric studies). Low heterogeneity was observed ($I^2 = 13.9$ %), reflecting methodological homogeneity among anatomical dissection studies. Individual estimates were tightly clustered, supporting the stability of the pooled prevalence.

3.3.6. *Diagnostic method subgroup: imaging-based studies*

Four imaging-based studies were included in this subgroup analysis [15,16,18,22]. The pooled prevalence was 0.08 % (95 % CI: 0.00–0.18 %), as shown in Fig. 9 (Prevalence in imaging-based studies). Substantial heterogeneity was observed ($I^2 = 71.5$ %), likely reflecting differences in imaging modalities, diagnostic criteria, and study populations. These findings highlight the influence of methodological variability on prevalence estimates derived from radiological assessments.

3.4. *Risk of bias of included studies*

Twenty-five studies met the assessment criteria using the AQUA Checklist for Anatomical Studies, which analyzed bias in five domains. Of these five domains, one study [15] presented a high risk of bias in the methodology and characterization domain, while two studies [14,18] presented a high risk of bias in the descriptive anatomy domain. Finally, in the results presentation domain, four studies [15,16,18,22] presented a high risk of bias, indicating that the results of at least seven studies should be interpreted with caution (Fig. 10).

3.5. *Anatomical and morphological considerations*

The close anatomical relationship between the atlas and the occipital bone explains the potential relevance of atlas occipitalization for the morphology and biomechanics of the craniovertebral junction. This congenital fusion anomaly may partially or completely restrict motion at the atlanto-occipital joint, leading to altered load transmission and changes in the dimensions of the foramen magnum [24]. Depending on the extent and configuration of the fusion, these anatomical modifications may affect the spatial relationships of adjacent neural and vascular structures, including the upper cervical spinal cord, vertebral arteries, and cervical nerve roots [25–27].From an anatomical and radiological standpoint, atlas occipitalization is frequently identified incidentally using computed tomography and magnetic resonance imaging. Accurate

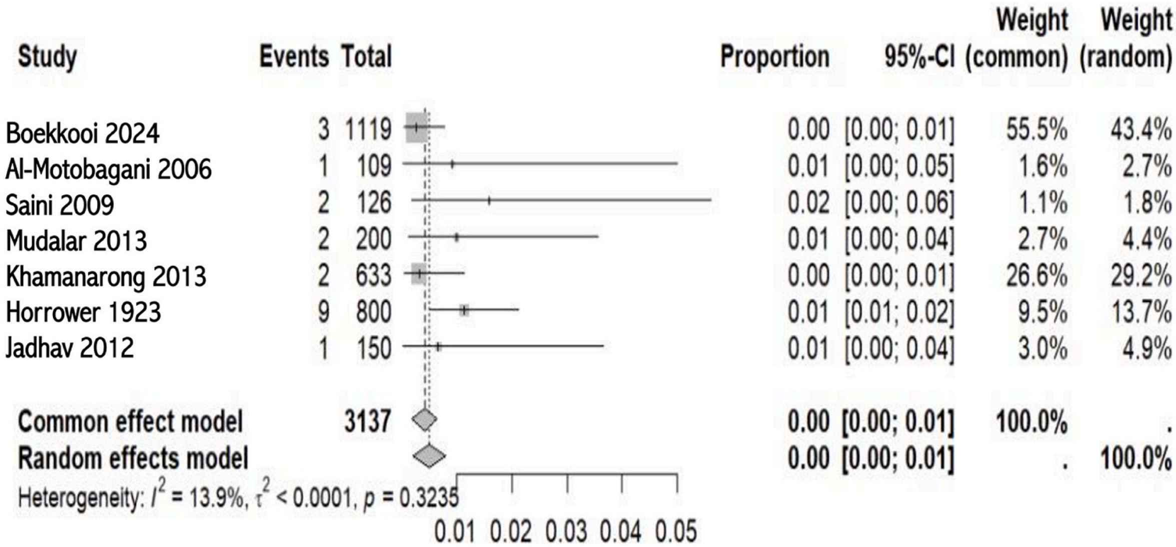

Fig. 8. Forest plot of the prevalence of atlas occipitalization in cadaveric studies.

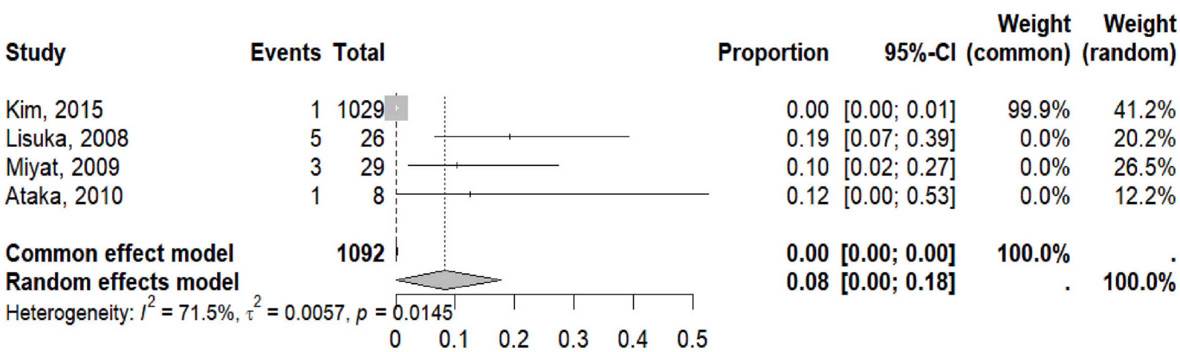

Fig. 9. Forest plot of the prevalence of atlas occipitalization in imaging-based studies.

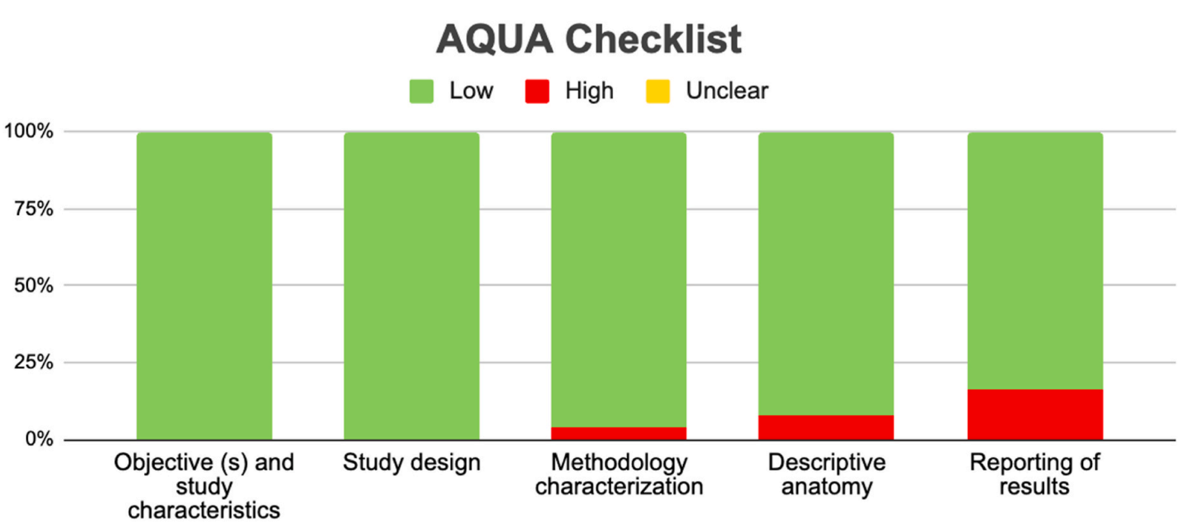

Fig. 10. AQUA checklist assessment of risk of bias across included studies.

recognition of this variant is essential, as fusion of the atlas to the occiput may obscure normal anatomical landmarks, modify vertebral artery trajectories, and complicate interpretation of craniovertebral anatomy. These features are particularly relevant for preoperative planning in posterior fossa and upper cervical spine procedures, where unrecognized anatomical variations may increase the risk of neurovascular injury [28–30]. Although atlas occipitalization is often asymptomatic, its clinical relevance may increase when associated with other craniovertebral junction anomalies, such as basilar invagination or Chiari type I malformation [31–33]. In these contexts, the loss of atlanto-occipital mobility may exacerbate neural compression, alter cerebrospinal fluid dynamics, and contribute to biomechanical instability of the craniovertebral junction. Stability in this region depends largely on ligamentous integrity rather than osseous congruence; therefore, congenital fusion combined with ligamentous laxity may predispose to abnormal motion and progressive neurological compromise [34,35]. Collectively, these considerations highlight the importance of detailed anatomical assessment and individualized interpretation of craniovertebral morphology in both diagnostic evaluation and surgical decision-making [3].

4. Discussion

This systematic review and meta-analysis provide a comprehensive synthesis of the available evidence on the prevalence of atlas occipitalization across different populations and methodological approaches. The pooled prevalence of 0.64 % confirms that atlas occipitalization is a rare congenital anomaly of the craniovertebral junction. Despite its low frequency, this anatomical variant remains relevant due to its potential implications for craniovertebral morphology, biomechanics, and neurovascular relationships.

4.1. Comparison with previous literature

Most previous investigations involving the craniovertebral junction have focused on surgical stabilization techniques and biomechanical performance rather than on population-based prevalence estimates. Studies evaluating posterior atlantoaxial fixation techniques have consistently reported high fusion success rates, highlighting the importance of anatomical variability at the craniovertebral junction during surgical planning [36]. Similarly, meta-analyses addressing vascular anatomical variants, such as high-riding vertebral arteries, emphasize the need for detailed anatomical assessment in this region, particularly in surgically treated populations [37].

In contrast, the present study contributes novel epidemiological insight by systematically synthesizing prevalence data for atlas occipitalization derived from both cadaveric and imaging-based investigations. This distinction is important, as atlas occipitalization represents a congenital anatomical variant rather than an acquired or surgically induced fusion, and its detection is strongly influenced by diagnostic methodology and study design [38].

4.2. Interpretation of prevalence and subgroup findings

The moderate heterogeneity observed in the overall meta-analysis ($I^2 = 47.4$ %) was anticipated given the diversity of study populations, geographic settings, and diagnostic approaches. Subgroup analyses demonstrated relatively consistent prevalence estimates among Asian populations; however, the lack of data from other geographic regions limits the ability to draw conclusions regarding global distribution patterns.

Sex-based subgroup analyses suggested a numerically higher prevalence in female subjects compared with males. Nevertheless, the overlap of confidence intervals and the absence of studies specifically designed to evaluate sex-related differences prevent definitive conclusions regarding true sexual dimorphism. Methodological factors exerted a notable influence on prevalence estimates. Cadaveric studies demonstrated low heterogeneity and consistent findings, reflecting methodological homogeneity and direct anatomical assessment. In contrast, imaging-based studies exhibited substantial heterogeneity, likely attributable to differences in imaging modalities, diagnostic criteria, and population characteristics. These observations underscore the importance of standardized diagnostic definitions when evaluating atlas occipitalization using radiological methods.

4.3. Anatomical and clinical implications

Although atlas occipitalization is frequently asymptomatic and often detected incidentally, its anatomical significance lies in its capacity to modify craniovertebral junction morphology and biomechanics. Fusion at the atlanto-occipital level may alter the spatial relationships of the foramen magnum, vertebral arteries, and upper cervical neural structures, potentially increasing susceptibility to neurological or vascular compromise, particularly when associated with additional craniovertebral anomalies such as basilar invagination or Chiari malformation [39–41]. Importantly, clinical severity does not consistently correlate with the extent of bony fusion, suggesting that individual neurovascular adaptation and compensatory mechanisms play a critical role in clinical expression [42].

From an anatomical perspective, accurate recognition of atlas occipitalization is essential for both diagnostic interpretation and surgical planning. While advances in imaging techniques have improved detection and classification of fusion patterns, anatomical dissection studies continue to provide complementary insights into morphological variability and spatial relationships that may not be fully captured by imaging alone [43–45].

5. Limitations

This systematic review has several limitations that should be considered when interpreting the findings. Publication bias cannot be excluded, as studies reporting low prevalence or incidental findings may be underrepresented in the literature. In addition, geographic representation was limited, with a predominance of studies conducted in Asia and North America, thereby restricting global generalizability. Variability in study design, diagnostic criteria, and reporting standards further limited direct comparisons across subgroups. Finally, most included studies were not primarily designed to assess prevalence, which constrains the strength of conclusions regarding regional, sex-based, or methodological differences. Future population-based studies employing standardized diagnostic criteria and broader geographic coverage are needed to better characterize the epidemiology and anatomical relevance of atlas occipitalization.

6. Conclusion

This systematic review and meta-analysis demonstrate that atlas occipitalization is a rare congenital anatomical variant of the craniovertebral junction, with a pooled prevalence of 0.64 %. Despite its low frequency, recognition of this variant remains relevant due to its potential influence on craniovertebral morphology and biomechanics, particularly when associated with other congenital anomalies such as basilar invagination or Chiari type I malformation.

The findings emphasize the importance of accurate anatomical and radiological identification of atlas occipitalization, especially in the context of preoperative planning at the craniovertebral junction. However, the limited geographic representation of available studies and the lack of standardized diagnostic criteria restrict the generalizability of current prevalence estimates. Future population-based investigations using uniform imaging definitions and broader regional inclusion are needed to better characterize the epidemiology and anatomical implications of atlas occipitalization.

Human participation declaration

This study was conducted exclusively through the analysis of previously published data. Therefore, ethical approval and informed consent were not required.

PRISMA declaration

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The completed PRISMA checklist is provided in Supplementary Table 2.

Ethical approval

As this study is a systematic review of published literature, approval from an institutional ethics committee was not required.

Human ethics statements and consent to participate

Not applicable.

Clinical trial registration

Not applicable.

Funding statement

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Funding statement

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CRediT authorship contribution statement

Alejandro Bruna-Mejias: Conceptualization, Methodology, Project administration, Resources. **Martina Salazar-Ferrari:** Conceptualization, Data curation, Validation, Visualization, Writing – original draft. **Antonia Silva-Garay:** Data curation, Resources, Software, Supervision. **Ignacia Belen Chacon Valdebenito:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision. **Cynthia Ortiz -Ahumada:** Conceptualization, Project administration, Software, Supervision, Validation. **Martin Trujillo-Riveros:** Conceptualization, Formal analysis, Investigation, Project administration, Software. **Jessica Paola Loaiza-Giraldo:** Conceptualization, Formal analysis, Investigation, Project administration, Software, Validation. **Pablo Nova-Baeza:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Software. **Mathias Orellana- Donoso:** Conceptualization, Data curation, Formal analysis, Project administration, Software. **Andres Santana- Machuca:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Gloria Cifuentes-Suazo:** Conceptualization, Data curation, Formal analysis. **Gustavo Oyanedel-Amaro:** Software, Supervision, Validation, Visualization. **Glen Paton:** Data curation, Funding acquisition, Methodology, Resources. **Shahed Nalla:** Conceptualization, Formal analysis, Investigation, Project administration, Software, Validation, Writing – original draft. **Juan José Valenzuela-Fuenzalida:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software. **Juan Sanchis-Gimeno:** Conceptualization, Data curation, Formal analysis, Methodology.

Declaration of competing interest

The authors of the manuscript; **"*Occipitalization of the atlas and its relationship with craniocervical clinical considerations. Systematic review with meta-analysis*"**declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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