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Machine learning or morphometric scaling? A systematic review of methodological confounds and the generalizability of sex classification in neuroimaging

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[Sapuan, Abdul Halim^a](#); [Jamaludin, Iqbal^a](#); [Majid, Zafri Azran Abdul^a](#); [Tamrin, Mohd Izzuddin Mohd^b](#); [Azemin, Mohd Zulfaazal Che^c](#) ; [+1 author](#)

^a Department of Diagnostic Imaging and Radiotherapy, Kulliyah of Allied Health Sciences, International Islamic University Malaysia, Kampus Kuantan, Pahang Darul Makmur, Kuantan, 25200, Malaysia

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Abstract

Background: This systematic review critically evaluates whether machine learning (ML) identifies biologically meaningful sex-related brain architecture or merely exploits methodological artifacts and allometric scaling. While ML models achieve high classification accuracies, it remains unclear if these reflect stable, mechanistically informative dimorphism or are driven by confounds such as total intracranial volume (TIV) and site-specific noise. We examine how imaging modalities, algorithms, and population strata influence both classification outcomes and biological interpretability. **Methods:** Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we searched Web of Science, PubMed, and Scopus through January 2024. Included studies [healthy humans, 3T magnetic resonance imaging (MRI), ML-based sex classification] were assessed for risk of bias, focusing on data leakage, validation strategies, and confound management. **Results:** Thirty-five studies ($n > 10,000$)

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[Corresponding authors](#)

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Authors (6)

[Sapuan, Abdul Halim^a](#)