

Sex Differences in the Neuropathology of Alzheimer's Disease: A Systematic Review



THE UNIVERSITY
OF BRITISH COLUMBIA
Faculty of Medicine

N. Catie Futhey¹, Jamie Marshall², Chloe Allen¹, Mark S. Cembrowski¹, Veronica Hirsch-Reinshagen¹

¹The University of British Columbia, Vancouver, BC, Canada; ²McGill University, Montréal, QC, Canada

Domain-specific sex differences are present across postmortem AD studies, with females showing greater tau, cerebrovascular, and TDP-43/LATE burden, and males showing greater Lewy body co-pathology on average. Methodological heterogeneity precludes formal pooling, underscoring the need for standardized, sex-disaggregated neuropathological frameworks in AD research.

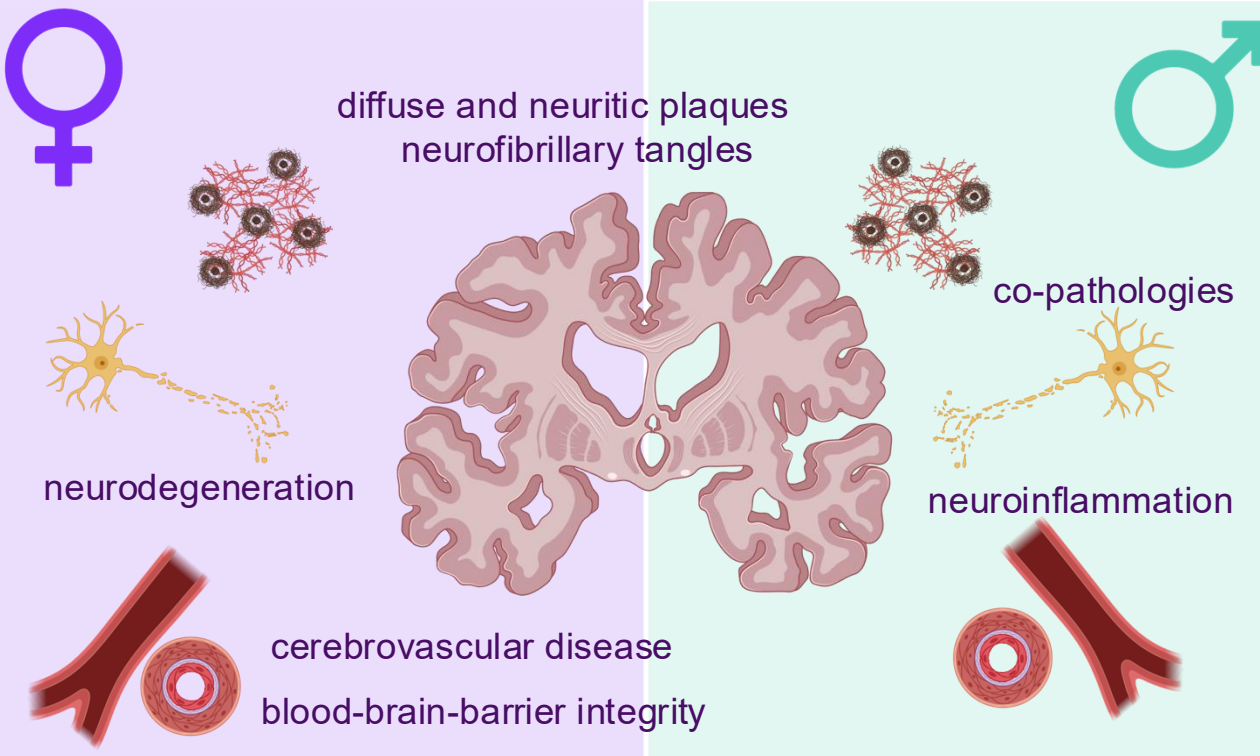
INTRODUCTION

Sex differences in Alzheimer’s disease (AD) prevalence, presentation, blood biomarkers, and clinical progression have been demonstrated.

Alzheimer's disease affects twice as many females.



Females experience more rapid cognitive decline and a unique menopause-related hormonal transition, which has well-characterized effects on neural, vascular, and immune aging.



These robust sex-specific trajectories may alter vulnerability to AD protein aggregation and cerebrovascular disease (CVD), yet **the effect of biological sex on postmortem AD neuropathology remains unclear.**

METHODS

A systematic review was conducted in accordance with PRISMA guidelines (PROSPERO registration CRD420251036390). Abstract and full-text screening, data extraction, and synthesis were performed independently by two reviewers.

Search Strategy
6 Databases: Embase, MEDLINE, Web of Science, PsycINFO, CINAHL, Cochrane Central Register of Controlled Trials

Eligibility Criteria
Studies published in English between January 1st 1994 and April 1st 2025 containing humans with autopsy-confirmed Alzheimer’s disease reporting sex- or hormone-stratified neuropathological outcomes.

INCLUDE

- ✓ Human patients with an autopsy-confirmed diagnosis of AD
- ✓ Reported by biological sex OR different hormonal subgroups (i.e., low vs. high testosterone, pre- vs. post-menopause)
- ✓ Outcome: postmortem neuropathology, protein expression, mRNA, or gross neuroanatomical changes

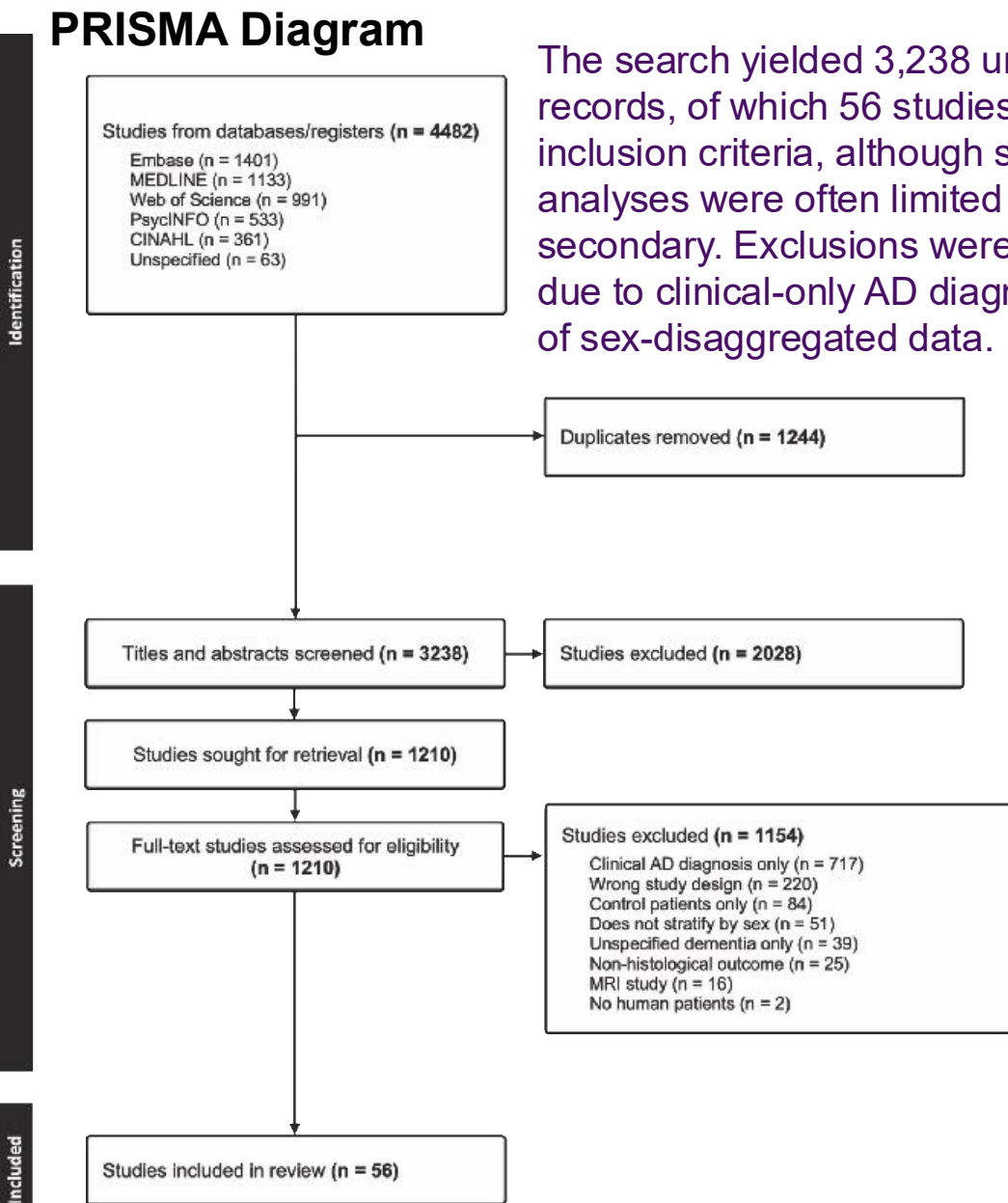
EXCLUDE

- ✗ Case reports, abstracts, editorials, letters, dissertations
- ✗ Animal or *in vitro* models
- ✗ Healthy controls only, unspecified or non-AD dementias
- ✗ Clinical diagnosis of AD only
- ✗ Does not provide separate analyses for male and female subjects

Primary outcomes: postmortem molecular and histopathological measures related to gross or microscopic anatomy, amyloid-β, tau, neurodegeneration, CVD, and/or concomitant proteinopathies.

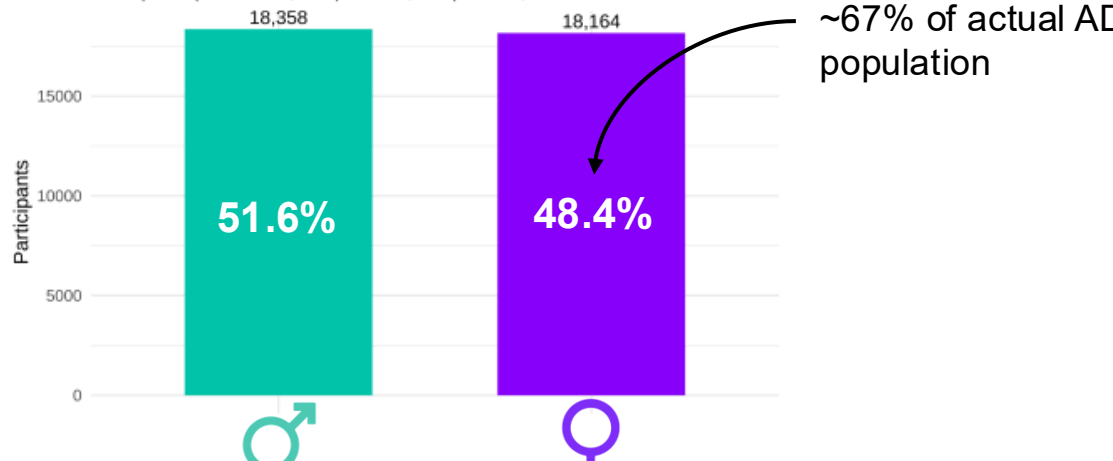
RESULTS

PRISMA Diagram



The search yielded 3,238 unique records, of which 56 studies met inclusion criteria, although sex-stratified analyses were often limited or secondary. Exclusions were primarily due to clinical-only AD diagnoses or lack of sex-disaggregated data.

Representation



Direction of Sex Differences in Neuropathology: Vote-Count Synthesis

	N (Studies)	F>M	M>F	F=M
Neurofibrillary Tangles (pTau)	9	8	0	1
Plaques (Aβ)	10	6	0	4
Cerebral Amyloid Angiopathy (CAA)	5	0	3	2
Cerebrovascular Pathology	5	4	1	1
Lewy Bodies (α-synuclein)	9	1	7	1
TDP-43/LATE	2	2	0	0
APOE ε4 Interaction	5	3	0	2
Synaptic Protein Expression	2	0	0	2
Neuroinflammation	2	2	0	0

CONCLUSIONS

This systematic review identifies a limited but informative literature on sex differences in AD neuropathology.

On average:

- Female Predominant** patterns include higher neurofibrillary tangles, parenchymal amyloid plaques, cerebrovascular pathology, and TDP-43/LATE co-pathology.
- Male predominant** patterns include Lewy body co-pathology.

These findings suggest **sex-specific vulnerability** in the type, distribution, and clinical relevance of AD pathology. Methodological heterogeneity across included studies, including variable inclusion criteria, cohort matching strategies, and outcome definitions, precludes quantitative synthesis and limits direct comparability.

Intentional, sex-disaggregated postmortem frameworks are urgently needed to refine AD staging criteria and inform sex-informed diagnostic and therapeutic targeting.

FUNDING & CONTACT



Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

This work was supported by a Canadian Institutes of Health Research Doctoral Canada Graduate Research Scholarship, the UBC MD/PhD Program, and the Martina A. Nash MD/PhD Scholars Endowment.

Graphics were created using BioRender.

catie.futhey@ubc.ca