

Gene-Environment Interactions in Dementia and Alzheimer's Disease: A Multidimensional Roadmap

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1. Introduction: The "Missing Heritability" Problem



Beyond Static Genetics

While GWAS identifies many risk loci, genetic factors alone do not explain the full incidence of Alzheimer's Disease, suggesting a massive role for Gene-Environment (GxE) interactions.

The "Exposome" Concept

The totality of environmental and social exposures (diet, pollution, education) that modify genetic risk across the lifespan.



57% Consensus: Over half of the analyzed literature strongly agrees that environmental and social factors significantly modulate genetic dementia risk.

2. Methods: PRISMA Systematic Search



Identification:

221,500 papers initially identified across Consensus, Publiht, and Semantic Scholar.



Multi-Phase Filtering



Papers screened for relevance and quality, narrowing the pool from 228 screened to 157 eligible studies.



Final Inclusion



50 high-quality papers (systematic reviews, GWAS, PRS, and MR studies) included in the final review.

3. Key Findings

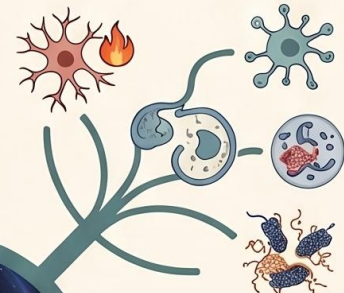
Branch: Ancestral Diversity

Impact varies by ancestry: *ABCA7* confers significantly higher risk in African Americans, while *APOE ε4*'s impact is often attenuated in certain African populations.



Branch: Biological Pathways

Genetic loci like *BIN1* and *PICALM* disrupt pathways involving neuroinflammation, lipid metabolism, endocytosis, and amyloid/tau processing.



Branch: Environmental Modifiers

Key modifiers include air pollution (PM_{2.5}/NO₂), Mediterranean diet adherence, sleep (REM/NREM disruption), and cognitive reserve (years of schooling).



Branch: Epigenetic Mediators

DNA methylation and histone acetylation act as "molecular switches," turning genes on or off in response to life stress or toxins without altering the DNA sequence.

4. Methodological Frontiers

MAGEE & Statistical Frameworks

Tools like MAGEE allow for large-scale sequencing analysis to detect subtle GxE effects and handle non-linear environmental exposures.



GxE-informed Polygenic Risk Scores (PRS)

Moving beyond simple additive models to scores that weight genetic variants based on their interaction with specific environmental factors for better risk prediction.

5. Research Gaps & Future Directions

Addressing Eurocentric Bias

	European	African	Asian	Longitudinal
GWAS Loci Discovery:	15	4	5	2
PRS Validation:	10	2	2	GAP
Cognitive Reserve:	8	1	GAP	GAP
Pollution Exposure:	6	2	GAP	GAP

Research Gap Matrix: Visualizing the lack of diversity in current GxE research.

Current data is heavily skewed, with 15 GWAS loci discovered in European cohorts compared to only 4 in African cohorts.



Toward "Precision Prevention"

Tailoring interventions—such as air filtration for those with high pollution sensitivity genotypes—rather than providing universal general advice.

6. Conclusion

GxE is Central to Etiology: Integrating precise environmental monitoring with diverse ancestral data is the cornerstone of effective 2030 dementia prevention.

“Precision in measuring the exposome must match genomic precision.”
Closing the gap between environmental tracking and genetic data is essential for equitable global brain health.

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