



Alzheimer's Disease Discordance In Monozygotic Twins: An Amyloid-confirmed Case Illustrating Divergent Life-course Exposure Profiles

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A unique natural experiment:
biomarker-confirmed, clinically discordant monozygotic (MZ) twin pair in their 50s.

BACKGROUND

Genetic factors account for ~50% of Alzheimer's disease (AD) risk. Up to ~50% of dementia cases may be attributable to modifiable risk factors across the life course. MZ twins discordant for AD provide a rare opportunity to examine how non-genetic factors may influence disease expression.

OBJECTIVE

To investigate the biological and life-history factors associated with early-onset AD in a biomarker-confirmed, clinically discordant MZ twin pair.

METHODS

Multimodal assessment

- Amyloid-β (Aβ) PET imaging
- ¹⁸F-FDG PET imaging
- Comprehensive neuropsychological testing
- Genetic screening (APOE genotyping and relevant AD genes panel)
- Structured life-history and psychosocial interviews

Both twins are male, in their 50s, and share identical germline genomes (APOE ε3/ε3).

	AFFECTED TWIN (AD)	UNAFFECTED TWIN (No AD)
	Male, 50s Clinically diagnosed AD Severe global cognitive impairment	Male, 50s Cognitively intact No cognitive impairment
AMYLOID-β PET	Aβ POSITIVE Diffuse cortical uptake	Aβ NEGATIVE No cortical uptake
¹⁸ F-FDG PET	Abnormal hypometabolism (AD-like pattern)	Normal metabolism
NEURO-PSYCHOLOGICAL PERFORMANCE	Severe impairment - Memory - Executive function - Language - Visuospatial skills - Global cognition	Average to superior performance - Memory - Executive function - Language - Visuospatial skills - Global cognition
GENETIC SCREENING	IDENTICAL GENETIC BACKGROUND APOE ε3/ε3 in both twins No pathogenic variants in APP, PSEN1, PSEN2 or other tested AD genes	

LIFE-HISTORY AND PSYCHOSOCIAL PROFILES	
AFFECTED TWIN (AD) Higher cumulative adversity	UNAFFECTED TWIN (No AD) Lower cumulative adversity
Bankruptcy and major financial stressors	Stable financial situation
Divorce and family estrangement	Stable long-term relationships and strong social support
Straight	Gay
Multiple sports-related concussions (hockey)	No history of significant head injuries
Chronic stress, anxiety and mood symptoms	Low stress, positive coping style
Reduced physical activity and social engagement over time	Sustained physical, cognitive and social engagement



Despite identical genomes, divergent life trajectories may have influenced brain health and AD pathogenesis.

KEY FINDINGS

Marked biological divergence:
The affected twin is Aβ positive with AD-typical hypometabolism and severe cognitive impairment, while the co-twin is Aβ negative and cognitively intact.

No genetic explanation:
Both twins are APOE ε3/ε3 and share identical germline genomes with no pathogenic variants in major AD genes—supporting a strong role for non-genetic factors.

Life-history divergence:
Cumulative psychosocial stressors and repeated head injuries in the affected twin contrast with stable support and healthy lifestyle in the unaffected twin.

CONCLUSION

This multimodal analysis of a biomarker-confirmed, clinically discordant MZ twin pair suggests that non-genetic factors—specifically cumulative psychosocial stress and physical trauma—may not merely modulate clinical reserve but actively influence the pathological onset of Alzheimer's disease.

IMPLICATIONS

- Highlights the potential impact of modifiable life-course exposures on AD.
- Supports integrated prevention strategies targeting stress reduction, brain injury prevention, and psychosocial well-being.
- Reinforces the need for personalized risk assessment *beyond* genetics.