

Antifungal drugs and the risk of Alzheimer's disease



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Take-Home Message: Our study, using a large Medicare sample, confirmed a strong association between fungal infections and AD risk in older adults. It also yielded new insights into the role of antifungal treatment in AD development. We found that treating mycoses with imidazoles and polyenes (two distinct classes of antifungal drugs) has an inverse association with AD risk, with imidazoles being AD-protective and polyenes detrimental. This antagonistic relationship warrants further investigation.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	DISCUSSION												
Accumulating evidence suggests that infections may increase Alzheimer’s disease (AD) risk. Our recent study found a significant association between history of fungal infections (mycoses) and AD risk (Ukraintseva et al., 2024, PMID: 38548241). Most such patients use antifungal drugs. Antifungal drugs have also been proposed as potentially protective against AD. But how does their purported AD-protective effect coincide with the overall elevated AD risk in individuals with a history of fungal infections? We hypothesized that different types of antifungal treatment may differ in their impact on AD risk, with some being protective and some others detrimental. To test this hypothesis, we explored associations of recurrent mycoses with AD onset, considering the use of different classes of anti-fungal medications.	We used sample of 1,114,845 Medicare beneficiaries aged 65+ , of which 830,329 had no record of a fungal infection (‘no mycoses’ group) and 284,516 were first diagnosed with a fungal infection in 2006 or later (‘mycoses’ group). We further split the mycoses group by the classes of antifungal drugs: i) imidazoles; ii) triazoles; iii) polyenes; iv) miscellaneous. A Greedy Propensity Score Matching (PSM) algorithm was used to identify a comparable group of non-mycoses controls. We used 1:1 matching without replacement based on propensity scores generated by a logistic model designed to estimate the probability of having a later life fungal infection using the 31 Elixhauser Comorbidity Index and available demographic variables.	We found that a history of recurrent fungal infections was associated with significantly higher AD risk (HR: 1.53; 95% CI: 1.50–1.56) after PSM, consistent with our earlier findings in HRS data (HR: 1.42; PMID: 38548241). Within the mycoses group, treatment with imidazoles (e.g., clotrimazole, miconazole, ketoconazole), was associated with reduced AD risk (HR: 0.89; 95% CI: 0.85–0.93), whereas treatment with polyenes (e.g., nystatin) was associated with increased risk (HR: 1.19; 95% CI: 1.15–1.23). <table><tr><th colspan="3">Table. Anti-Fungal Treatment and Alzheimer's Disease Risk (HR)</th></tr><tr><th>Drug classes</th><th>Mycoses, Full Sample</th><th>Mycoses, Treated Sample</th></tr><tr><td>Imidazoles only</td><td>0.89 [0.85-0.93]**</td><td>0.92 [0.86-0.97]**</td></tr><tr><td>Polyenes only</td><td>1.19 [1.15-1.23]**</td><td>1.25 [1.18-1.31]**</td></tr></table>	Table. Anti-Fungal Treatment and Alzheimer's Disease Risk (HR)			Drug classes	Mycoses, Full Sample	Mycoses, Treated Sample	Imidazoles only	0.89 [0.85-0.93]**	0.92 [0.86-0.97]**	Polyenes only	1.19 [1.15-1.23]**	1.25 [1.18-1.31]**	Our study, using Propensity Score Matching applied to a 5% Medicare sample, confirmed a strong significant association between fungal infections and AD risk in older adults. It also yielded new insights into the role of antifungal treatment in AD development. Treating mycoses with imidazoles and polyenes (two distinct classes of antifungal drugs) showed a significant inverse association with AD risk, with imidazoles being AD-protective and polyenes detrimental. Our findings encourage deeper research into the mechanisms by which different classes of antifungal drugs influence AD development and how they may interact with other AD risk factors. Such knowledge is vital for advancing personalized AD prevention.	The trade-off-like effect of imidazoles and polyenes (two distinct classes of antifungal drugs) on AD risk warrants further investigation. The absolute effect was larger for polyenes than for imidazoles, which may partly explain why the protective effect of imidazoles coincides with the overall elevated AD risk among individuals with a history of recurrent fungal infections. Acknowledgements This research was supported by the National Institutes of Health's National Institute on Aging (NIA/NIH) grant R01AG076019. This content is solely the responsibility of the authors and does not necessarily represent the official views of the NIA/NIH. This study was conducted using de-identified 5% sample of U.S. Medicare beneficiaries. ALZHEIMER'S ASSOCIATION AAIC 26
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