view_only=74556323721b4f7ba49acffbb3cb9ead.

1. Schumacher L, Klein JP, Hautzinger M et al. World Psychiatry 2024;23:411-20.
2. Falkenström F, Finkel S, Sandell R et al. J Consult Clin Psychol 2017;85:537-49.
3. Borsboom D. World Psychiatry 2017;16:5-13.
4. Lunansky G, Bonanno GA, Blanken TF et al. Psychol Rev 2025;132:1396-409.
5. van Bork R, Lunansky G, Borsboom D. Measurement 2024;232:114643.

DOI:10.1002/wps.70021

Sex modifies the relationship between depression and risk for dementia: implications for targeted prevention

Alzheimer's disease and related dementias (ADRD) are projected to affect 13.8 million Americans by 2060, with women comprising nearly two-thirds of those diagnosed[1]. Depression, a highly prevalent and modifiable risk factor, is nearly twice as common in women and has been independently linked to elevated ADRD risk[2-4]. Yet, the joint effect of sex and depression on cognitive decline remains under-explored in large-scale longitudinal studies.

We analyzed 75,069 visits from 11,091 participants aged 65 and older, using data from 42 Alzheimer's Disease research centers across the US. The final sample had a mean of 9.71 visits (SD=3.43; range: 2-19) over an average follow-up period of 3,679 days, equivalent to approximately 10 years (range: 5-18 years). We used Cox proportional hazards models to examine time to cognitive impairment, defined as a clinical diagnosis of mild cognitive impairment or dementia, in relation to Geriatric Depression Scale (GDS-15) score, sex, age, and apolipoprotein E ε4 (APOE ε4) genotype. For ease of interpretation, depression was coded as binary (depressed: GDS-15 score ≥5; not depressed: GDS-15 score <5).

Controlling for age and APOE ε4 genotype, depression increased the risk of cognitive impairment by 77% in men (hazard ratio, HR= 1.77, 95% CI: 1.68-1.87, p<0.001) and by 119% in women (HR=2.19, 95% CI: 2.02-2.38, p<0.001). The interaction between depression and sex was statistically significant (HR=1.24, p<0.001). While women had lower baseline hazard of cognitive impairment (HR= 0.62), they experienced a disproportionately greater increase in impairment risk when depressed.

We then used a time-varying covariate model, which accounts for changes in depression status across repeated observations, to test whether risk trajectories differed over time. In this model, at baseline, men with depression had a 165% higher risk of cognitive impairment (HR=2.65), while women had only a 19% increase (HR=1.19). The depression-sex interaction was HR=0.45. However, over time, men who became depressed were 23% less likely to develop cognitive impairment, while women who became depressed were 19% more likely to develop impairment at some point. Therefore, the depression-sex interaction at follow-up became HR=1.55 (95% CI: 1.12-2.15, p<0.01). This suggests that depression that emerges or persists later in life may have a more harmful effect on women's brain health than men's. Importantly, these effects remained consistent across older age groups, indicating that the depression-sex interaction is stable across the later life course.

In additional analyses, we modeled depression continuously and found that each additional point on the GDS-15 increased the risk of cognitive impairment by approximately 14.5% (HR=1.14, 95% CI: 1.139-1.150, p<0.001). We also categorized depression severity into three groups using GDS-15 scores: normal (0-4), mild (5-8), and moderate-to-severe (9-15). Our analyses showed a clear dose-response relationship between depression severity and risk of cognitive impairment. Mild depression was associated with a 69% increased risk (HR=1.69; 95% CI: 1.57-1.82), while moderate-to-severe depression increased risk by 80% (HR=1.80; 95% CI: 1.59-2.04). Importantly, time-varying effects indicated that the impact of moderate-to-severe depression slightly increased over time (p<0.001), suggesting cumulative risk, whereas the impact of mild depression remained stable. These results were adjusted for age, APOE ε4 genotype, and accounted for time effects, underscoring the importance of recognizing even mild depression as a significant and clinically actionable ADRD risk factor.

To assess the robustness of our findings, we conducted several sensitivity analyses. First, we examined attrition bias, and found that dropout rates were low and comparable between sexes (men: 1.6%, women: 1.5%, p=0.72). Next, we assessed baseline depression severity, finding that men had slightly higher mean GDS-15 scores than women (4.14 vs. 4.02; Wilcoxon W=110,604,030, p< 0.001). We conducted an additional test to assess significant differences in depression severity by sex: for the 6,186 observations in the depressed group, there were none (W=4,475,864, p=0.07). Therefore, any sex differences in cognitive impairment predicted by depression are not driven by differences in depression severity between groups. Third, we accounted for center-level differences, by including ADRD research center-level frailty terms in all models. Finally, we expanded the sample to include participants under age 65, and found that the depression-by-sex interaction remained significant (HR=1.22, p<0.001).

Together, these results indicate that sex modifies the relationship between depression and ADRD, and that this effect is not due to measurement or sampling bias, but likely reflects a biologically meaningful difference. Several mechanisms could account for women's heightened susceptibility to cognitive impairment. Compared to men, women with depression may exhibit greater neuroinflammatory responses[5], more rapid hippocampal atrophy[6], and heightened hypothalamic-pituitary-adrenal axis dysregulation[7], all of which may magnify the long-term neurodegenerative impact of depression.

Clinically, our findings support the prioritization of depression screening and treatment as a key strategy for ADRD prevention, especially for women. Despite global efforts[8,9], sex remains underutilized as a stratifying factor in both research and practice. Fur-

thermore, depression is often treated as a static covariate in models of cognitive decline, despite being dynamic and potentially interactive.

We offer the following recommendations for future research and clinical care: a) routine screening and early intervention for depression, especially in mid- to late-life women; b) inclusion of sex-stratified and interaction models in ADRD risk prediction and observational research; c) clinical trials of depression treatment that examine cognitive outcomes by sex across the lifespan; d) mechanistic studies exploring sex-specific inflammatory, hormonal, and stress-related pathways linking depression and neurodegeneration.

In sum, our longitudinal analysis of over 75,000 visits across US Alzheimer's Disease research centers revealed that depression significantly increases ADRD risk for both sexes, but the trajectory and magnitude differ by sex. The interaction between sex and depression persists across time, analytic methods, and population subsets. Women with depression are at disproportionately higher risk for cognitive impairment as they age. These findings underscore the urgency of tailoring ADRD prevention strategies to account for sex-specific vulnerabilities.

Lauren A. Rutter[1], Lucas J. Hamilton[2], Skylar Wilson[1], Anne C. Krendl[1], Brea L. Perry[3]
[1]Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN, USA; [2]Department of Psychology, Augustana University, Sioux Falls, SD, USA; [3]Department of Sociology, Indiana University, Bloomington, IN, USA

The US National Alzheimer's Coordinating Center (NACC) database is funded by the US National Institute on Aging/National Institutes of Health (NIA/NIH) (grant no. U24 AG072122). NACC data are contributed by the NIA-funded Alzheimer's Disease research centers. L.A. Rutter and B. Perry are supported by NIA grants (respectively, no. K01 AG086598 and no. R01 AG057739).

1. Alzheimer's Association. Alzheimers Dement 2023;19:1598-695.
2. Livingston G, Huntley J, Sommerlad A et al. Lancet 2020;396:413-46.
3. Ownby RL, Crocco E, Acevedo A et al. Arch Gen Psychiatry 2006;63:530-8.
4. Salk RH, Hyde JS, Abramson LY. Psychol Bull 2017;143:783-812.
5. Mac Giollabhui N, Ng TH, Ellman LM et al. Mol Psychiatry 2021;26:3302-14.
6. Diniz BS, Teixeira AL, Machado-Vieira R et al. J Gerontol B Psychol Sci Soc Sci 2014;69:845-51.
7. Maekawa K, Yamanaka K. Clin Exp Neuroimmunol 2023;14:100-9.
8. Mielke MM, Vemuri P, Rocca WA. Clin Epidemiol 2014;6:37-48.
9. Ferretti MT, Iulita MF, Cavedo E et al. Nat Rev Neurol 2018;14:457-69.

DOI:10.1002/wps.70022

Nutritional psychiatry on the move: the activities of the ECNP Nutrition Network to leverage nutrition for brain health

Brain health is a pressing global concern[1]. Neurodevelopmental and mental disorders are leading causes of disability. As the population continues to grow and age, the number of individuals affected by dementia worldwide is expected to rise significantly. While evidence-based interventions for mental disorders are available, challenges persist, particularly as not all patients respond to current pharmacological or psychological treatments.

Our limited understanding of psychiatric conditions and their treatment stems from major gaps in knowledge of the underlying neurobiological mechanisms. Emerging research suggests that the pathophysiological underpinnings of mental disorders can extend beyond the central nervous system. Compelling evidence indicates that disorders such as major depression should be viewed as whole-body conditions that entail both central processes, such as changes in neurotransmitter systems and reduced neuroplasticity, and peripheral factors resulting from the involvement of the immune and neuroendocrine systems. Immune activation interacts with metabolic and endocrine systems that control energy homeostasis, as shown by significant associations between inflammatory markers (C-reactive protein, interleukin-6) and higher body mass index, fat mass, triglycerides, as well as lower HDL cholesterol in large-scale studies. Thus, metabolic and immune dysregulation are intertwined, prompting research to explore biomarkers of this combined dysregulation[2].

We are beginning to recognize that nutrition might help close the prevention and treatment gap in mental disorders. Poor diet quality is a major environmental risk factor for brain disorders and one of the few that are modifiable[3]. While evidence continues to grow on the impact of nutrition across the life course, we are still far from fully harnessing its potential to improve mental health conditions.

The field of nutritional psychiatry has recently gained momentum, driven by a surge in observational and intervention studies supporting a role for diet in managing psychiatric symptoms[4]. At the same time, epidemiological research highlights unhealthy eating as a growing risk factor for metabolic and brain health. Additionally, data indicate that obesity and metabolic conditions deriving from the use of medications, such as antipsychotics, present challenges for clinicians, reinforcing the need for an approach to mental disorders that considers brain and body health as a unique integrated system.

Individual nutrient needs are shaped by physical and psychological health, habitual diet and lifestyle, and differ across the life course and in response to environmental factors. One of the main challenges that nutritional psychiatry currently faces is the lack of conclusive evidence that diet and nutrition impact mental health. Overall, randomized controlled trials (RCTs) investigating dietary change in treatment of mental disorders remain limited, although some report significant improvements in mood and reduced anxiety in adults[5]. Not all studies reproduced these findings, underscoring the need to replicate, refine and scale-up dietary intervention research for prevention and treatment.

The Nutrition Network of the European College of Neuropsychopharmacology (ECNP) was established with the main mission to better understand the bidirectional links between mental health and nutrition, including the mediating systems, to inform novel