factors may contribute to sex differences in ADRD. Using the Health and Retirement Study (N = 9908, European ancestry), a US panel-cohort study, the current analysis leverages Mendelian randomization techniques to assess sex-specific inferred causality of depressive symptoms on odds of dementia. All analyses assess most recent cognition and account for sex, education, study cohort, age and year of most recent cognition visit, and genetic ancestry principal components. A one standard deviation increase in depressive polygenic score was associated with 1.11 times higher odds of dementia (95% confidence interval: 1.02-1.21) relative to normal cognition. Each additional endorsed depressive symptom was associated with 1.13 times higher odds of dementia (95% confidence interval: 1.09-1.18) relative to normal cognition. Using the depression genetic instrument, a significant inferred causal relationship was observed between depressive symptoms and dementia (P=0.01, 1.73 odds ratio, 95% confidence interval: 1.12-2.67). When stratified by sex, this relationship was only significant in females (P=0.02, 1.76 odds ratio, 95% confidence interval: 1.08-2.87). These findings demonstrate that depressive symptoms are likely causally related to dementia, and this relationship is most pronounced in females.

DEPRESSION AND PSYCHOLOGICAL WELL-BEING AS DISTINCT CONSTRUCTS: MUTUALLY EXCLUSIVE ASSOCIATIONS WITH BIOMARKER

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Despite increasing emphasis on assessing the mental health of older adults, there has been inconclusive evidence on whether depression and psychological well-being (PWB) are fundamentally distinct constructs or representations of the opposite ends of the mental health spectrum. To instantiate either hypothesis, investigation of the associations between mental health scales and biomarkers have been proposed. First, we assessed depressive symptoms and PWB in community-dwelling older adults (N=59, mean age=67) using the Self-Rating Depression Scale (SDS) and Ryff's Scale of PWB (comprising six sub-scales). We measured a wide range of immune markers employing ELISA and flow cytometry. Subsequently, we used principal component analysis (PCA) to aggregate and derived biomarker factor scores. Lastly, multiple linear regressions were performed to examine the associations between the scales and the derived biomarker factor scores, controlling for covariates. PCA extracted six biomarker factors. Biomarker factor score 1 was significantly associated with PWB (β=-0.029, p=0.035) and the PWB sub-scale, self-acceptance (β=-0.089, p=0.047), while biomarker factor score 4 was significantly associated with the PWB sub-scale, purpose in life (β=-0.087, p=0.025). On the other hand, biomarker factor 6 was significantly associated with SDS (β=-0.070, p=0.008). There were mutually- exclusive associations between the scales with biomarker factor scores, supporting the hypothesis of distinct constructs. Our findings expanded the biomarkers of depression and PWB, deepening understanding of the biological underpinnings of depressive symptoms and PWB. These findings have implications in field work, since researchers could not infer one construct from the other, the examination of both constructs are essential.

LIFESTYLE COMPLEXITY AND DEMENTIA RISK: EXAMINING MODERATION BY APOE GENOTYPE AND MILD COGNITIVE IMPAIRMENT

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Prior studies suggest that the neuroprotective effect of physical exercise is moderated by APOE genotype and MCI status, but it remains unclear whether this extends to lifestyle complexity defined by a broader variety of physical, intellectual, and social activities. Participants were from the Ginkgo Evaluation of Memory (GEM) Study. We used 18 physical, intellectual, or social activities from the Lifestyle Activity Questionnaire. We performed latent class analysis to characterize subgroups with distinct activity response patterns and examined whether they have differential risk of incident dementia over time. A three-class model was chosen based on fit statistics and interpretability. Cox proportional hazards models, adjusted for potential demographic and health confounders, revealed that Class 1 (Highly intellectually/socially active) had a reduced risk of dementia compared to Class 3 (Less socially/less intellectually active; HR=.71, 95% CI: [.56,.88], p=.002). Class 2 (Socially/less intellectually active) did not differ in risk from Class 3 (HR=.90, 95% CI: [.73,1.1], p=.288). There was no evidence for effect modification for APOE e4 allele carriers (p's>.05), but the protective association for Class 1 only held for those without prevalent MCI at baseline (HR=.74, 95% CI: [.56,.98], p=.033). Results showed that subgroups characterized by a greater variety of social and intellectual activities had reduced risk for dementia, but only for those without MCI. This implies that late-life lifestyle complexity may be most neuroprotective for those in the preclinical stages of decline. Results also suggested that lifestyle complexity may act through a cognitive reserve pathway unrelated to amyloid pathology.

MIDLIFE PLASMA Aβ AND LATE-LIFE RISK OF COGNITIVE IMPAIRMENT: THE ATHEROSCLEROSIS RISK IN COMMUNITIES STUDY

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