Muscle Protects Brain

Lean mass protective against Alzheimer's

Currently, there are no reliable treatments for Alzheimer's disease, which means our best approach is to focus on prevention. Approximately one-third of individuals with Alzheimer's disease have risk factors that can be modified, such as obesity, inflammation, insulin resistance, and elevated levels of amyloid B in fat tissue. As a result, we must question if increasing lean mass can reduce our risk and whether exercise can offer protection, and what type of exercise offers protection. This study examines the links between these factors to determine if higher lean mass can help prevent Alzheimer's disease.

Abstract

Objective To examine whether genetically proxied lean mass is associated with risk of Alzheimer's disease.

Design Mendelian randomisation study.

Setting The UK Biobank study and genome wide association study meta-analyses of Alzheimer's disease and cognitive performance.

Participants Summary level genetic data from: 450 243 UK Biobank participants with impedance measures of lean mass and fat mass; an independent sample of 21 982 patients with Alzheimer's disease and 41 944 controls without Alzheimer's disease; a replication sample of 7329 patients with Alzheimer's disease and 252 879 controls; and 269 867 individuals taking part in a genome wide association study of cognitive performance.

Main outcome measure Effect of genetically proxied lean mass on the risk of Alzheimer's disease, and the related phenotype of cognitive performance.

Results An increase in genetically proxied appendicular lean mass of one standard deviation was associated with a 12% reduced risk of Alzheimer's disease (odds ratio 0.88, 95% confidence interval 0.82 to 0.95, P=0.001). This finding was replicated in an independent cohort of patients with Alzheimer's disease (0.91, 0.83 to 0.99, P=0.02) and was consistent in sensitivity analyses that are more robust to the inclusion of pleiotropic variants. Higher genetically proxied appendicular lean mass was also associated with increased cognitive performance (standard deviation increase in cognitive performance for each standard deviation increase in appendicular lean mass 0.09, 95% confidence interval 0.06 to 0.11, P=0.001), and adjusting for potential mediation through genetically proxied cognitive performance did not reduce the association between appendicular lean mass and risk of Alzheimer's disease. Similar results were found for the outcomes of Alzheimer's disease and cognitive performance when the risk factors of genetically proxied trunk lean mass and whole body lean mass were used, respectively, adjusted for genetically proxied fat mass.

Conclusions These findings suggest that lean mass might be a possible modifiable protective factor for Alzheimer's disease. The mechanisms underlying this finding, as well as the clinical and public health implications, warrant further investigation.

Prior research has examined the link between body mass index (BMI) and the risk of Alzheimer's disease but didn't find any evidence of a causal relationship. However, in this study, researchers analyzed data from over 450,000 participants in the UK Biobank, including more than 320,000 individuals with and without Alzheimer's disease, and almost 270,000 people participating in a separate genes and intelligence study. They discovered over 500 genetic variants linked to lean mass in the extremities. Employing Mendelian randomization, a technique that employs measured variation in genes of known function to examine the causal effect of a modifiable exposure on disease in observational research, they investigated the causal impact of the risk factor using genetic variants reliably related to a modifiable risk factor.

Through human genetic data, they discovered evidence for a protective effect of lean mass on the risk of Alzheimer's disease. Lean mass is a proxy for muscle mass, defined as the difference between total mass and fat mass, and is lower in patients with and who developed Alzheimer's disease than in controls. Higher appendicular (extremity) lean mass was

linked to higher levels of cognitive performance. This study focused only on the relationship with Alzheimer's type dementia, not other forms of dementia.

What does this imply for us? There may be a protective impact of lean mass on the development of Alzheimer's disease and reduced cognitive performance. It's critical to ensure that we maintain or increase our lean (muscle) mass as part of our long-term health maintenance. It's not just necessary for our functional status but also for our cognitive status. So, grab some weights and get started!

Daghlas I, Nassan M, Gill D. Genetically proxied lean mass and risk of Alzheimer's disease: mendelian randomisation study. *BMJ Medicine* 2023;**2:**e000354. doi: 10.1136/bmjmed-2022-000354