



Association of genetic predisposition to dyslipidemia and physical activity with incident dementia

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Genetic predisposition to dyslipidemia is associated with an increased risk of dementia. Across different levels of this genetic predisposition, physical activity is associated with a lower dementia risk, especially for vascular dementia.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS
Elevated serum low-density lipoprotein cholesterol (LDL-C) in midlife is a recognized predictor of future dementia risk, but evidence linking genetically determined dyslipidemia to dementia remains inconsistent. Using dyslipidemia polygenic risk scores (PRS) to capture lifelong genetic susceptibility, we investigated their association with incident dementia and whether a physically active lifestyle is associated with a lower dementia risk across all strata of genetic predisposition.	We analyzed 198,448 White participants aged 60 years and older from the UK Biobank over a median follow-up of 14.8 years. Using Cox proportional hazards models, we assessed the associations between dyslipidemia PRS, self-reported physical activity, and the risk of incident all-cause dementia, Alzheimer’s disease (AD), and vascular dementia (VaD). All models were adjusted for age, sex, educational attainment, socioeconomic status, <i>APOE</i> ε4 carrier status, and genetic principal components.	Higher LDL-C PRS and lower high-density lipoprotein cholesterol (HDL-C) PRS were associated with an increased risk of incident all-cause dementia, AD, and VaD. Being physically active was associated with a lower risk of all-cause dementia and VaD. This beneficial association of a physically active lifestyle was consistently observed across all genetic risk strata for both lipid traits and was most pronounced for VaD. LDL-C PRS Physical activity Low Active Inactive Intermediate Active Inactive High Active Inactive All-cause dementia VaD AD HR (95% CI) HR (95% CI) HR (95% CI) HDL-C PRS Physical activity High Active Inactive Intermediate Active Inactive Low Active Inactive All-cause dementia VaD AD HR (95% CI) HR (95% CI) HR (95% CI) <td> Genetic predisposition to higher LDL-C and lower HDL-C is associated with an increased dementia risk. Physical activity represents a promising preventive strategy, even for individuals with a high genetic susceptibility to dyslipidemia. </td>	Genetic predisposition to higher LDL-C and lower HDL-C is associated with an increased dementia risk. Physical activity represents a promising preventive strategy, even for individuals with a high genetic susceptibility to dyslipidemia.
REFERENCES			
Liang Y, Xie S, Sheng D, Ding L, Yang T, Jia J. Association of genetic predisposition to dyslipidemia and physical activity with incident dementia. <i>Alzheimers Dement</i>. 2026;22(1):e71079. doi:10.1002/alz.71079			
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Genetic predisposition to higher LDL-C and lower HDL-C is associated with an increased dementia risk. Physical activity represents a promising preventive strategy, even for individuals with a high genetic susceptibility to dyslipidemia.

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