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TITLE: Do modifiable risk factors moderate the effect of APOE on cognitive decline?

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ABSTRACT:
There is an extensive literature examining gene-environment interactions (GxE) on psychopathology, such as risk from individual genes being moderated by modifiable risk factors. The general pattern emerging from this literature is that GxE effects fail to replicate across samples/research groups. One possibility for failed GxE replications may be that a vast majority of genes associated with psychopathology confer very small risk, and prior studies have been underpowered for GxE investigations. Importantly, the ApoE gene, linked to dementia, stands in stark contrast to other psychopathology-linked genes. Specifically, heterozygotes for the ApoE risk polymorphism (ε4) have a three-fold increase in risk and homozygotes have a 15-fold increase in risk for developing late-onset dementia (vs. ε3/ε3—those with no risk polymorphisms). Thus, the ApoE gene presents a unique opportunity to examine GxE effects with modifiable factors (e.g., diet, exercise), thereby informing patient decision making regarding their lifestyle. We applied survival analyses to the UK Biobank (n=417,323; *M* age=66) to examine ApoE-by-modifiable risk effects on dementia. First, main effect suggested that modifiable factors can increase dementia risk, including: current depression, history of depression/anxiety, diabetes, pack

years of cigarette use, and body mass index. Further, some modifiable factors may decrease dementia risk, including: grip strength, vitamin D levels (via blood test), education, social support, and hormone replacement therapy (in women only). Finally, after correcting for multiple testing, interaction models suggested that the risk conferred by the ApoE gene varied as a function of participant education. Specifically, ApoE risk was attenuated as participant educational attainment increased.

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