

# Identifying modifiable factors and their joint effect on dementia risk in the UK Biobank

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Previous hypothesis-driven research has identified many risk factors linked to dementia. However, the multiplicity and co-occurrence of risk factors have been underestimated. Here we analysed data of 344,324 participants from the UK Biobank with 15 yr of follow-up data for 210 modifiable risk factors. We first conducted an exposure-wide association study and then combined factors associated with dementia to generate composite scores for different domains. We then evaluated their joint associations with dementia in a multivariate Cox model. We estimated the potential impact of eliminating the unfavourable profiles of risk domains on dementia using population attributable fraction. The associations varied by domain, with lifestyle (16.6%), medical history (14.0%) and socioeconomic status (13.5%) contributing to the majority of dementia cases. Overall, we estimated that up to 47.0%–72.6% of dementia cases could be prevented.

Dementia is a leading cause of disability and dependency in older people<sup>1</sup>. Given the lack of effective treatments, exploring modifiable risk factors to design preventive measures is an important, perhaps only current way available to reduce dementia burden<sup>2</sup>. In the past decades, hypothesis-driven methods have been commonly adopted to explore the modifiable factors<sup>3–12</sup> that could be integrated into dementia prevention packages. However, these methods have several limitations. First, single-exposure analyses are highly likely to produce overestimated effect sizes and type I errors due to the interconnected nature of risk factors<sup>13</sup>. Second, these studies contain selective reporting constraining reproducibility<sup>14</sup>. Third, investigating one or a handful of risk factors at a time cannot reflect the synergistic effects of exposures, which is also important owing to the multifactorial nature of late-life dementia<sup>4</sup>. Lastly, single-exposure analyses have not shed light on the overall contribution of risk factors to dementia, which

has currently gained considerable attention as recent randomized controlled trials have shown the effectiveness of multidomain lifestyle interventions for dementia prevention<sup>2</sup>.

An exposure-wide association study (EWAS) is a hypothesis-free strategy that systematically and agnostically investigates the relationship between multiple variables and a single outcome. Researchers have successfully applied this technique to complex diseases other than dementia, including depression<sup>15</sup>, HIV<sup>16</sup> and diabetes<sup>17</sup>. By investigating a wide range of exposures simultaneously, EWAS validates established factors from previous studies with reduced bias and false-positive findings<sup>13,18</sup> while enabling the discovery of novel risk factors<sup>19</sup>. The analytic rational, similar to genome-wide association study (GWAS), employs standardized analytical procedures and generates results with greater robustness compared with hypothesis-driven approaches<sup>18</sup>. Moreover, by constructing composite scores<sup>4</sup> and calculating a population

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