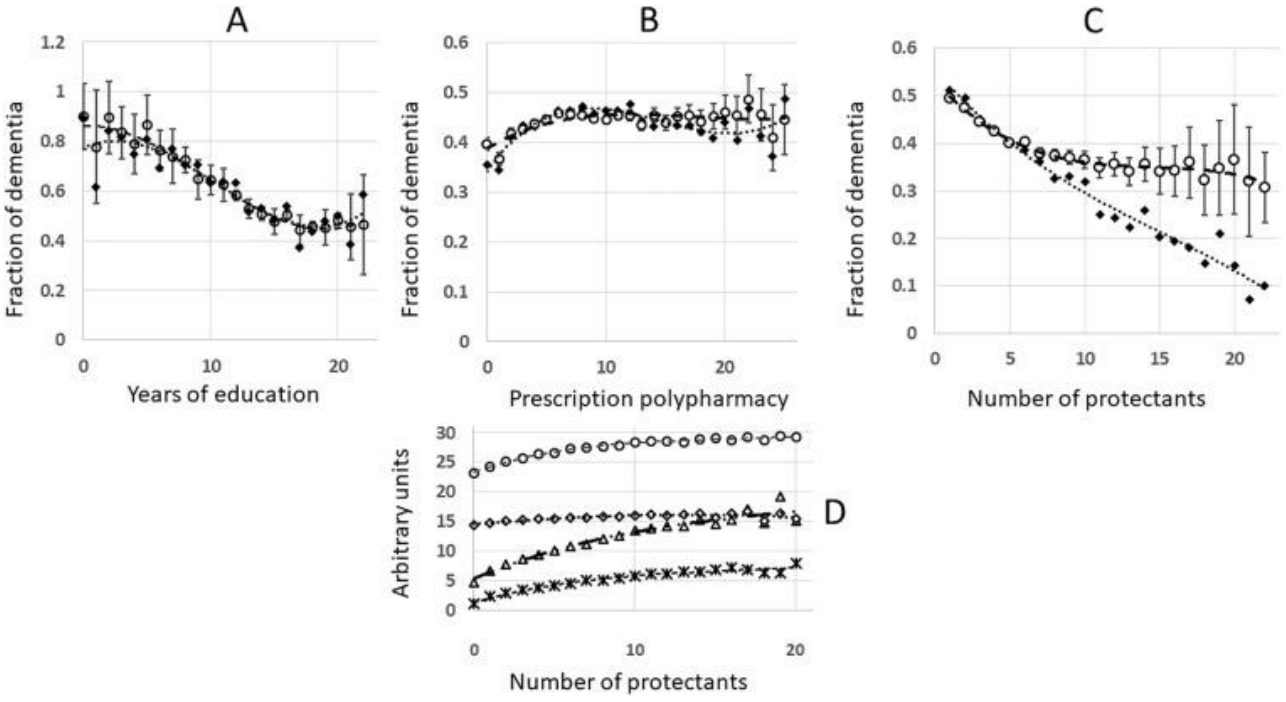
Preventive treatments for dementia are warranted. Here we show that utilization of certain combinations of prescription medications and supplements correlates with reduced rates of cognitive decline. More than 1,900 FDA-approved agents and supplements were collapsed into 53 mechanism-based groups and traced in electronic medical records (EMRs) for >50,000 patients. These mechanistic groups were aligned with the data presented in more than 300 clinical trials, then regression model was built to fit the signals from EMRs to clinical trial performance. While EMR signals of each single agents correlated with clinical performance relatively weakly, the signals produced by combinations of active compounds were highly correlated with the clinical trial performance (R = 0.93, p = 3.8 x10^-8). Higher ranking pharmacological modalities were traced in patient profiles as their combinations, producing protective complexity estimates reflecting degrees of exposure to beneficial polypharmacy. For each age strata, the higher was the protective complexity score, the lower was the prevalence of dementia, with maximized life-long effects for the highest regression score /diversity compositions. The connection was less strong in individuals already diagnosed with cognitive impairment. Confounder analysis confirmed an independent effect of protective complexity in multivariate context. A sub-cohort with lifelong odds of dementia decreased > 5-folds was identified; this sub-cohort should be studied in further details, including controlled clinical trials. In short, our study systematically explored combinatorial preventive treatment regimens for age-associated multi-morbidity, with an emphasis on neurodegeneration, and provided extensive evidence for their feasibility.

Figure 1



**Background models constructed by combining potential confounders.**

A. Testing background model in NACC (38837 patients). Fraction of dementia at the end of follow-up was plotted as a function of educational achievement, years. Hollow circles symbolize the background model, combining all confounders. Diamonds symbolize observed values. B. Testing background model in NACC (38837 patients). Fraction of dementia at the end of follow up is plotted as a function of prescription polypharmacy actives per a person. Hollow circles symbolize the background model, combining all confounders. Diamonds symbolize observed values. C. Plotting of dementia at the end of follow up as a function of protectant number in NACC. Hollow circles symbolise the background model combining all confounders in a multivariate context, diamonds symbolize the observed dementia values. D. Distribution of potential confounders as a function of protective complexity in NACC. Hollow circles symbolize MMSE cognitive score at baseline, diamonds–years of education, triangles–polypharmacy at baseline, number of prescriptions, star symbol–length of follow up, years.