

Modifiable Risk Factors for Dementia by Frailty: Application of Population Intervention
Effects

by

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Defense Date: April 1st, 2024

Approved:

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Lijing Yan

Thesis submitted in partial fulfillment of
the requirements for the degree of Masters of Science in the Department of Global Health in the
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ABSTRACT

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Abstract

Background

Several modifiable risk factors for dementia have been identified. Rising interests focus on how frailty captures heterogeneous treatment and prevention effects. This study aimed to examine the association between modifiable risk factors and all-cause dementia among middle-aged and older adults and compare population-level intervention effects across frailty status.

Methods

Participants from UK Biobank without dementia and with available data on frailty and modifiable risk factors at baseline were included. Dementia was ascertained from inpatient records. Frailty was defined by a modified version of physical frailty phenotype and classified as non-frail, pre-frail and frail. Thirteen socioeconomic, life-style, environmental, and medical risk factors were included. We used Logistic regression to examine their association with 10-year dementia. Population intervention effects were also estimated by parametric G-computation.

Results

Of 381, 419 eligible participants with a mean age of 56.9 years, 58.4%, 38.2%, and 3.4% were non-frail, pre-frail, and frail, respectively. Over a 10-year follow-up, 1,688 (0.76%), 1,949 (1.34%), and 378 (2.90%) dementia cases were identified among non-frail, pre-frail, and frail adults. The odds ratios for low education, physical inactivity, central obesity, hearing impairment, high NO₂ exposure, and traumatic brain injury increased with higher frailty levels, but those for smoking, depression, hypertension, and diabetes decreased. Population intervention effects for single risk factors (excluding smoking and excessive alcohol use) increased with severer frailty

status. For interventions achieving 100% coverage, the population intervention effect was 0.002, 0.007, and 0.022 in the non-frail, pre-frail, and frail populations, respectively. Even with intervention coverage of only 25% and 50%, the population intervention effect remained highest among the frail population.

Conclusion

We found that frailty modifies the associations between established risk factors and dementia among middle-aged and older adults. Dementia intervention effectiveness appears to be greatest among frail adults. Therefore, routine frailty evaluation should be adopted to identify those who will gain the most from personalized dementia prevention strategies.

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Acknowledgements

Special thank you to my advisor Prof. Chenkai Wu for guiding this research, along with his research assistant Junhan Tang for supporting my reaserch a lot.

1. Introduction

Dementia is an irreversible and progressive decline in cognitive function and in the ability to live independently due to nerve degeneration. [1]. In 2019, the global population living with dementia was estimated at 57.4 million, with projections indicating a rise to over 150 million by 2050, mainly attributed to the aging population [2]. Dementia exerts a considerable economic toll, surpassing \$1.3 trillion annually on a global scale. This places significant strains on families and healthcare systems internationally [3]. At present, existing medications solely mitigate symptoms associated with dementia, while they do not reverse or stop the progression of dementia [4, 5]. Hence, there is a prioritized focus on addressing modifiable risk factors for dementia prevention.

The Lancet Commission has identified 12 modifiable risk factors for dementia based on a life-course perspective and suggested that about 40% of dementias could be averted through the targeting of these factors [6]. However, the effectiveness of intervening on these known risk factors within the heterogeneous older adults remains uncertain, since their health conditions are vastly different.

Recently, rising amounts of studies have focused on examining varied treatment effects in clinical studies and heterogeneous associations in observational studies according to certain individual characteristics [7, 8]. Frailty, an age-associated syndrome defined by decreased ability to withstand stressors and heightened susceptibility to negative outcomes, is posited as a potential rationale for health heterogeneity among older adults. [9, 10]. Some post-hoc analyses of

randomized controlled trials have indicated that frailty may alter both pharmaceutical and non-pharmaceutical treatment effectiveness among adult patients [11, 12]. Similarly, numerous observational studies have revealed significant heterogeneity in the associations between exposure and outcome based on different frailty levels[13-16]. Therefore, we are interested in whether and in what manner frailty modifies the association between established modifiable risk factors and dementia. Answering this question will help identify populations who would gain most from public health strategies based on modifiable risk factors, and also pave the way for targeted interventions and precision population health.

In addition to applying traditional regression models to gauge the association strength between risk factors and dementia, intervention effectiveness within specific populations is often incorporated when considering preventive strategies. The most common example is the calculation of population attributable fractions [6, 17, 18]. In present study, we adopted the concept of population intervention effects (PIEs). In randomized controlled trials, particularly those using intention-to-treat analysis, the average treatment effect is commonly employed to estimate the average difference in outcomes between patients receiving therapy and those not. A more generalized term of this effect is known as the population average causal effect. It compares two populations: one entirely exposed to a certain factor and another entirely unexposed, thereby is classified as an exposure effect [19]. However, completely exposed scenarios are rare in the real world, limiting the applicability of this concept when devising population-level policies. Conversely, another epidemiological effect, the population intervention effect, is better suited for addressing population intervention issues [19]. It measures the health benefits to the population with observed, factual exposure distributions resulting from varying degrees of exposure

alterations (elimination or reduction of exposure). Unlike exposure effects, population intervention effects often depend on the population prevalence of exposure.

We attempted to use a causal inference approach called G-computation to obtain population intervention effects. It is well acknowledged that observational studies have a critical limitation in causal inference due to the absence of information under counterfactual exposure scenarios [20]. For example, in the real world, investigators can only observe a participant being smoker (or not smoker) and whether dementia occurs later on. However, the opposite exposure status, not smoker (or smoker), and the corresponding dementia outcome in that person cannot be simultaneously observed. These missing information hinders direct causal effects estimation. G-computation, a maximum likelihood estimator of the G-formula, can predict outcomes in counterfactual scenarios in observational studies, so as to approximate the parameters obtained in a randomized controlled trial. Therefore, under specific assumptions, it enables interpreting results from observational studies causally [20]. G-computation is highly flexible and can be based on various common statistical models, such as logistic regression [20]. However, this technique has been limitedly applied in estimating population intervention effects. A study by McQuade et al. provides a reference in this regard [21].

In the present study, employing data of a large number of participants in UK Biobank, we first aimed to examine the association between 13 modifiable risk factors and 10-year all-cause dementia among middle-aged and older adults across frailty status (non-frail, pre-frail, and frail). Then, we second aimed to use parametric G-computation to determine the PIEs.

2. Methods

2.1 Data Source

UK Biobank is an open-access, ongoing national prospective cohort study that enrolled over 500,000 individuals aged 37-73 during the period from 2006 to 2010. These participants underwent assessments at one of 22 designated centers in the UK. These assessments included a touch-screen questionnaire, a face-to-face interview conducted by nurses, physical measurements, and the gathering of biological specimens at the baseline period [22]. Throughout the UK, participants' medical and health-related records were followed up. Especially, hospital inpatient records and the linkage to the National Death and Cancer Registry were available during the follow-up [23]. Prior to participation, all individuals provided electronic informed consent for the collection, analysis, and usage of data. Ethical approval for the UK Biobank study was obtained from the North West-Haydock Research Ethics Committee (REC reference: 16/NW/0274). Further elaboration on the study design and data acquisition is available elsewhere.²⁶ This study is part of the UK Biobank project 51450.

2.2 Analytic sample

502,412 participants were initially included. After exclusion of 11,701 participants due to missing frailty data, 108,847 participants with lacking data on at least one modifiable risk factor, along with 445 participants diagnosed with dementia at baseline, 381,419 participants finally remained in the analytical sample.

2.3 Dementia

The outcome was all-cause dementia over 10 years including Alzheimer's dementia, vascular dementia, other types of dementia, and unspecified dementia. Based on the 10th version of the International Classification of Diseases (ICD10), inpatient records identified dementia cases and onset dates. We ascertained events occurring after 10 years from the date of baseline.

2.4 Frailty

Frailty was evaluated using the physical frailty phenotype (PFP) method originally formulated by Fried and his team[24]. The definition in our study was a version tailored to adapt to the data collection approach of UK Biobank [25]. PFP comprises five criteria: slowness, weakness, exhaustion, inactivity, and shrinking. We categorized individuals as non-frail, pre-frail, and frail based on whether they met 0, 1-2, and 3-5 criteria, respectively.

The "slowness" was satisfied when the participants responded with "Slow" to the question, "How would you describe your usual walking pace?". For the "weakness", participants were considered to fulfill if handgrip strength was below or equal to sex- and body mass index-specific cut-points. The "exhaustion" criterion was fulfilled if participants reported feeling tired or having little energy "Nearly every day" or "More than half the days" over the past two weeks. The "inactivity" criterion was satisfied if participants engaged in no or light activity once per week or less. The shrinking criterion was fulfilled if the responses were "Yes, lost weight" to the question, "Compared with one year ago, has your weight changed?". Detailed explanation of these definitions were shown in Table S1.

2.5 Modifiable Risk Factors

We included 13 modifiable risk factors (air pollution in the Lancet Commission review was separated as two air pollutants) and modeled them dichotomously: low education, physical inactivity, smoking, central obesity, social isolation, hearing impairment, depression, hypertension, diabetes, excessive alcohol use, high NO₂ exposure, high PM_{2.5} exposure, and traumatic brain injury.

Their definitions were as follows: (1) Education attainment was created by self-reported acquirement of educational qualifications: CSEs, O-levels, A-levels, college or university degree, NVQ, HND, NHC, or equivalent, other professional qualification, and none of these. Education attainment below a college or university degree was defined as low education [26]. (2) Physical activity level was calculated based on the intensity, duration, and frequency of physical activity over the previous four weeks. Total weekly leisure-time activity of less than 500 Met-minutes was considered physical inactivity [27, 28]. (3) Smoking status was self-reported and had three categories, never, previous, or current smoking. Current smoking was defined as a risk factor [29]. (4) Based on the baseline measurement of waist and hip circumference, we determined participant's waist-to-hip ratio (WHR). Central obesity was defined as $WHR \geq 0.9$ in men or ≥ 0.85 in women [30]. (5) Following a prior study [31], a social isolation score ranging from 0 to 3 was generated. This score was derived from responses to three questions concerning cohabitants, visiting friends and family, and social activities. A total score greater or equal to 2 indicated social isolation. (6) Participants were asked if they had hearing problems in or not in a noisy environment. Hearing impairment was ascertained if they answered yes despite in or not in a noisy environment. (7) Participants provided information on whether they had consulted a

psychiatrist due to depression, anxiety, nerves, or tension [29]. Additionally, a Patient Health Questionnaire-2 (PHQ-2) scale was included in the questionnaire. Depression was defined if they had a visit or their PHQ-2 score was not less than 2 [32]). (8) Hypertension status was confirmed if participants reported a diagnosis of hypertension, used antihypertensive medication, or had an inpatient record of hypertension diagnosis. (9) Diabetes was ascertained if they self-reported a diagnosis of diabetes or insulin use, or if an inpatient record indicated diabetes [33]. (10) Weekly alcohol consumption was calculated based on participants' self-reported frequency, types, and quantity of alcohol drinking [30]. Participants were classified as excessive alcohol users if their consumption exceeded 14 units per week, as per the National Health Service (NHS) drinking guidelines [34] (11) The average annual exposure of NO₂ at participants' residential address in 2010 was estimated using a Land-using Regression model in UK Biobank[35] and categorized into quartiles by us. The exposure level over the lowest quartile was considered as high NO₂ exposure [6]. (12) High PM_{2.5} exposure was defined following the methods for NO₂. (13) Traumatic brain injury cases were identified from inpatient records.

2.6 Covariates

Four demographic covariates were considered: age in years, sex, ethnicity (classified as Whites or Others, as commonly done in UK Biobank), and the Townsend deprivation index [36]. A comorbidity index comprising 17 health conditions was developed using ICD10 and ICD9-CM codes [37, 38]. The cognitive ability at baseline was calculated based on the results of reasoning, pairs matching, reaction time, and prospective memory [39]. Additionally, the APOE ϵ 4 genotype was identified by Affymetrix using a BiLEVE Axiom array in the UK Biobank [40].

2.7 Analytic Approach

Initially, we conducted a descriptive analysis to compare baseline characteristics between the included and the excluded individuals. Then, within the analytical sample, we stratified individuals by frailty status and described their characteristics respectively. Continuous variables were summarized using means and standard deviations, while categorical variables were presented as counts and percentages. We employed analysis of variance for continuous variables and chi-squared tests for categorical variables to assess differences by frail status. Within each frailty stratum, participants were further classified into two subgroups for each modifiable risk factor, based on the presence or absence of risk factors. We compared the crude 10-year dementia incidence risks between these subgroups. Multivariable logistic regression models adjusted for covariates were used to examine the associations between modifiable risk factors and 10-year dementia among each frailty group.

The PIE can be interpreted as the average risk difference of 10-year all-cause dementia between the population with factual exposure distribution and the population with expected exposure distribution after intervention [21]. For each modifiable risk factor, participants were categorized as either having or not having the risk factors, termed as uncovered or covered, respectively. We explored three intervention scenarios for each modifiable risk factor among the uncovered individuals: altering exposure status from exposed to unexposed for random 25% of the uncovered individuals (25% coverage), altering exposure status from exposed to unexposed for random 50% of the uncovered individuals (50% coverage), and altering exposure status from

exposed to unexposed for all uncovered individuals (100% coverage). The process of randomly selecting participants was conducted independently for each risk factor and only for uncovered individuals.

We employed G-computation to estimate PIEs [20]. Using observed data, we calculated β -coefficients for each variable by fitting the logistic regression model mentioned above (referred to as “Q-model”) for each frailty stratum. Utilizing the β -coefficients estimated, we calculated a probability of dementia occurrence within 10 years for each participant. In accordance with each intervention scenario, we created a new dataset to simulate the exposure distribution after intervention, while holding all the covariates constant. Utilizing this new dataset, we predicted a new probability of having dementia for each participant. Then, we calculated and averaged the difference between observed and predicted probabilities across all participants. This risk difference served as the estimation of 10-year dementia risk reduced by intervention, namely the PIE in this study. To estimate the confidence interval for each PIE, we performed a non-parametric bootstrap with 500 repetitions. We first estimated PIEs and corresponding confidence intervals of targeting single modifiable risk factors, then targeted all modifiable risk factors together to estimate the overall effect.

All analyses were performed in Stata 17.0. and R 4.1.2.

3. Results

3.1 Sample Characteristics

Among the 381,419 participants analyzed, 58.4% were classified as non-frail, 38.2% as pre-frail, and 3.4% as frail. The mean ages for these groups were 56.7, 57.2, and 58.0 years, respectively, with varying percentages of females (52.5%, 57.7%, and 63.4%) (Table 1). Frail individuals, compared to non-frail counterparts, were less likely to be of White ethnicity and had lower economic status. They exhibited higher prevalence of comorbidity, low education, physical inactivity, social isolation, traumatic brain injury, hearing impairment, depression, central obesity, hypertension, and diabetes. Additionally, they also had a higher probability to smoke and have high exposure to PM_{2.5} or NO₂. Compared with excluded individuals, the prevalence of most modifiable risk factors was higher among included individuals, particularly low education, hearing impairment, central obesity, depression, diabetes, and hypertension. (Table S1).

3.2 Associations of Modifiable Risk Factors with Dementia

Over the 10-year follow-up period, 4,015 cases of all-cause dementia were identified, representing 1.05% of the total sample. Among these cases, 1,688 (0.76%), 1,949 (1.34%), and 378 (2.90%) came from non-frail, pre-frail, and frail participants, respectively (Table 2). Among the entire sample, all modifiable risk factors, with the exception of excessive alcohol consumption, demonstrated associations with a heightened 10-year risk of dementia. The minimal risk difference was 0.13% for depression, while the largest risk difference was 1.86% observed in traumatic brain injury.

Subsequently, stratified by frailty status, we conducted a comparison of the 10-year dementia risk difference between participants with and without each risk factor. (Table 2). Across the spectrum of frailty levels (non-frail, pre-frail, and frail), with the exceptions of smoking, depression, and excessive alcohol use, the disparity in risk widened for 10 modifiable risk factors (low education, physical inactivity, central obesity, social isolation, hearing impairment, hypertension, diabetes, high NO₂ exposure, high PM_{2.5} exposure, and traumatic brain injury).

After incorporating these risk factors into logistic regression models with demographic and health covariates, the trends of odds ratios for most risk factors were consistent with risk differences. However, for hypertension and diabetes, the association attenuated significantly across frailty levels, with the ORs (CIs) being 1.18 (1.06-1.31) and 1.70 (1.41-2.04) in the frail and decreasing to 1.08 (0.85-1.37) and 1.44 (1.12-1.86) in the non-frail, respectively. The high PM_{2.5} exposure appeared to no longer be associated with dementia in all strata. (Table 3).

3.2 Population Intervention Effects (PIEs)

We observed a rise in the PIE across different levels of frailty in all three intervention scenarios, where all risk factors were targeted jointly (Figure 1). For an intervention of 25% coverage (i.e., randomly changing exposure status for 25% of participants with each risk factor), the PIE was 0.001 (95% CI 0.0008, 0.0012) among the non-frail, 0.002 (0.001, 0.003) among the prefrail, and 0.008 (0.005, 0.011) among the frail. Similar trends were shown with larger intervention coverages. With interventions targeting 50% of uncovered participants, the PIE was 0.001 (0.0004, 0.0016) for the non-frail, rising to 0.004 (0.003, 0.005) for the pre-frail and 0.014

(0.010, 0.019) for the frail, respectively. Achieving 100% coverage resulted in PIEs of 0.002 (0.001, 0.003) for non-frail participants, 0.007 (0.006, 0.008) for pre-frail participants, and 0.022 (0.017, 0.027) for frail participants.

We also calculated the PIE targeting each risk factor individually (Figure 2). For the intervention targeting 25% of uncovered participants, the PIE for low education, central obesity, social isolation, hearing impairment, high NO₂ exposure, physical inactivity, hypertension, diabetes, high PM_{2.5} exposure, and traumatic brain injury increased with frailty being severe. These PIEs surged particularly when the prefrail progressed to the frail, while the magnitudes of increase differed by risk factors. A more substantial difference in PIE was observed for the same risk factors when the intervention coverage reached 50% and 100%.

4. Discussion

Using a comprehensively phenotyped cohort comprising a sizable sample of frail individuals, this study investigated whether the routine frailty evaluation can be used to identify individuals whose dementia risk might be reduced most effectively by intervening with known modifiable risk factors. Three notable findings stand out for discussion. First, the association between most modifiable risk factors and dementia was modified by frailty, except for excessive alcohol use and high PM_{2.5} exposure. Notably, stronger association in 7 risk factors (i.e., low education, physical inactivity, central obesity, hearing impairment, high NO₂ exposure, and traumatic brain injury), but weaker association in remaining 4 risk factors (i.e., smoking, depression, hypertension, and diabetes) was found with higher frailty levels. Second, frail population had the most substantial PIE (i.e., largest risk reduction) when interventions were applied to 10 of these modifiable risk factors individually. Third, when all modifiable risk factors were simultaneously addressed, the PIE rose gradely with frailty being severe.

The modifiable risk factors for dementia in this study have been widely investigated [6, 41]. Overall, our results support previous evidence. However, the magnitudes of association we found were slightly lower than the relative risks calculated by the Lancet Commission [6]. On the one hand, it is possible that part of the associations were mediated by frailty. Previous research has found that almost half of protective effect of healthy lifestyles on dementia was mediated by lower frailty [42]. On the other hand, an important reason was that we used relatively loose thresholds to define risk factors.

Most importantly, we found that frailty modified the association between these risk factors and dementia. For the majority of risk factors, we observed the strongest association among frail individuals. These findings align with several studies investigating the modifying effects of frailty on the effectiveness of both prevention and treatment. For instance, Eckel and colleagues demonstrated that frailty could exacerbate the lung function repairment caused by ozone or PM₁₀ exposure among a large amount of older adults [43]. Pandey et al. conducted a post-hoc analysis of a clinical trial among heart failure patients, and found that frail patients derived a greater rate reduction of hospitalization after aerobic exercise training [11]. A secondary analysis in Mexico also revealed that the association between smoking and increased mortality risk was only significant among individuals with the most severe frailty [15]. A possible explanation is that frail persons have pool ability to cope with outside stressors because of diminished physiological reserve and therefore might be more susceptible to risk factors.

However, we also found attenuated associations in smoking, depression, hypertension, and diabetes, which might imply they are less influential for frail individuals. Similar effects were observed in two studies suggesting a higher frailty level could moderate genetic risks for dementia [42] and the relationship between Alzheimer's disease pathology and dementia [44]. Their explanation, frailty might decrease the threshold of these factors causing dementia, may also be applicable to our results, although we did not focus on genetic and pathological factors. Notably, considering smoking, hypertension and diabetes are all cardiovascular risk factors, and frailty is mostly associated with vascular dementia [45, 46], there might be an underlying mechanism between frailty, cardiovascular factors, and dementia, which require further elucidation. Taken together, the modifying effect of frailty contrasts with a previous study that

found associations were attenuated with age for most risk factors [26]. This reflects that frailty can capture health heterogeneity beyond chronological ages.

If eliminating these modifiable risk factors (i.e., 100% intervention coverage) in combination among the frail population, the risk reduction would be approximately 10 times greater than among the non-frail population. Even with only a 25% intervention coverage for each risk factor, the frail population would experience a considerably higher absolute risk reduction. Although G-computation did not allow us to directly estimate population attributable fraction, comparing the PIE with total 10-year dementia risk provides insights. The PIE in the frail population accounted for larger proportion of the total dementia risk (e.g., PIE of 100% intervention coverage: total risk equals 0.022: 0.029) than in the non-frail population (0.002: 0.011). This suggests that interventions may reduce the largest proportion of dementia risk in the frail population. Therefore, public policies addressing these risk factors are expected to benefit more among people with frailty in the real world, both on an absolute and relative scale.

When targeting each single risk factor, the PIE still dramatically increased with frailty in most risk factors. However, the magnitudes of increase varied, resulting in different relative contributions of each risk factor in non-frail and frail populations. Among all, physical inactivity contributed the most to total PIE in the frail population, not only due to its increased risk but also because it had a very high prevalence as a component of frailty. Noteworthy, although hypertension, diabetes, and depression appeared to be less influential with worse frailty status on the individual level, population-level interventions targeting these three risk factors would still

yield greater risk reduction among the pre-frail and frail, primarily due to the substantial increase in prevalence. Therefore, public policies for frail population cannot ignore these factors.

Overall, our results highlight that the variability in the association between established risk factors and dementia across different frailty levels. Particularly, addressing these factors resulted in a substantially larger dementia risk reduction among frail individuals. First, these findings complement existing evidence on the complex relationship between frailty and dementia [47]. While frailty has been shown to predict dementia independent to known risk factors [22], we further revealed frailty can also alter the risks due to other risk factors towards different direction, suggesting frailty may change some mechanisms contributing to dementia. Second, our results again emphasize the critical need for targeting modifiable risk factors in dementia prevention, particularly among persons with frailty. Notably, considering many risk factors for dementia are shared by frailty [48, 49], early intervention becomes imperative. Third, our findings underscore the potential utility of routine frailty assessment in both community and hospital settings to identify high-risk population who would gain the most by intervening on socio-economic, lifestyle, environmental, and medical risk factors. A recent viewpoint has stressed the significance of implementing a routine frailty evaluation in different clinical settings, which is crucial for advancing frailty-guided disease management strategies [50]. However, the frailty assessment rates in clinic still need to be improved especially among specialties other than geriatricians [51].

Our study has several strengths. As far as we know, this is the first study to examine the modifying effect of frailty on the association between risk factors and dementia, involving a large

sample size with available frailty information. Additionally, the G-computation approach enables us to estimate the risk reduction among populations with factual exposure distributions under varied intervention coverages, which is more applicable in real-world scenarios. We acknowledge several limitations in our study. First, part of UK Biobank participants were relatively young at baseline. As a result, although the follow-up was 10 years long, it might be inadequate to detect dementia incidence for them. Future cohort studies involving older participants and longer follow-up are necessary to validate our results. Second, we only included 13 well-established modifiable risk factors summarized by the Lancet Commission. However, previous research has identified a broader spectrum of risk factors [52]. The modifying effect of frailty on other risk factors needs to be examined in future studies. Third, the risk factors might change over time, while we only considered them at baseline. Future studies could employ repeated assessment design to provide deeper insights. Fourth, while other mainstream frailty assessment tools are available[53, 54], we only used the PFP method. Future studies could evaluate the modification of frailty using other definitions. Lastly, all dementias in our study were identified from inpatient records, mainly representing severe cases. Consequently, the association between risk factors and mild dementia may not be fully elucidated. Subsequent investigations with more comprehensive definitions of dementia will help explain a more complete relationship.

5. Conclusion

In summary, our study offers new insights into the modification of frailty on the associations between known modifiable risk factors and dementia among middle-aged and older adults. Through the application of an advanced statistical technique, we demonstrate that the effectiveness of interventions based on modifiable risk factors for dementia may differ depending on frailty levels. Our findings underscore leveraging routine frailty assessments in clinical and public health settings to identify those who will gain the most from personalized prevention strategies.

Appendix: Tables and Figures

Table 1. Baseline characteristics by frailty status.

Characteristics	Non-frail N=222,740	Pre-frail N=145,663	Frail N=13,016	<i>P</i> value*
Age, mean (SD)	56.7 (8.0)	57.2 (8.1)	58.0 (7.6)	<0.001
TDI, mean (SD)	-1.7 (2.8)	-1.0 (3.2)	0.5 (3.5)	<0.001
Cognitive score, mean (SD)	3.4 (2.1)	3.7 (2.3)	4.2 (2.4)	<0.001
Female, n (%)	116,992 (52.5)	84,065 (57.7)	8,250 (63.4)	<0.001
Ethnicity, n (%)				<0.001
White	214,521 (96.6)	135,423 (93.3)	11,447 (88.4)	
Others	7,613 (3.4)	9,773 (6.7)	1,507 (11.6)	
APOE e4 carrier, n (%)	56,818 (25.5)	36,656 (25.2)	3,190 (24.5)	<0.001
Comorbidity, n (%)				<0.001
None	199,407 (89.5)	120,688 (82.9)	8,125 (62.4)	
One or more conditions	23,333 (10.5)	24,975 (17.1)	4,891 (37.6)	
Education, n (%)				<0.001
College or university	77,046 (34.6)	39,850 (27.4)	2,053 (15.8)	
Others	145,694 (65.4)	105,813 (72.6)	10,963 (84.2)	
Physical inactivity, n (%)	137,308 (61.6)	105,101 (72.2)	12,226 (93.9)	<0.001
Smoking, n (%)				<0.001
Never or previous	202,670 (91.0)	128,577 (88.3)	10,513 (80.8)	
Current	20,070 (9.0)	17,086 (11.7)	2,503 (19.2)	
Central obesity, n (%)	103,061 (46.3)	80,136 (55.0)	8,829 (67.8)	<0.001
Social isolation, n (%)	55,033 (24.7)	38,436 (26.4)	3,585 (25.5)	<0.001
Hearing impairment, n (%)	88,097 (39.5)	65,488 (45.0)	7,271 (55.9)	<0.001
Depression, n (%)	79,946 (35.9)	71,855 (49.3)	8,859 (68.1)	<0.001
Hypertension, n (%)	57,491 (25.8)	52,703 (36.2)	7,090 (54.5)	<0.001
Diabetes, n (%)	7,181 (3.2)	11,662 (8.0)	2,626 (20.2)	<0.001
Excessive alcohol use, n (%)	118,494 (53.2)	63,650 (43.7)	3,660 (28.1)	<0.001
NO ₂ , mean (SD)	26.0 (7.5)	27.1 (7.6)	28.8 (7.8)	<0.001
PM _{2.5} , mean (SD)	9.9 (1.0)	10.0 (1.1)	10.3 (1.1)	<0.001
Traumatic brain injury, n (%)	345 (0.2)	267 (0.2)	40 (0.3)	<0.001

Abbreviations: SD, standard deviation; TDI, Townsend deprivation index.

* Obtained from the analysis of variance or χ^2 tests.

Table 2. Crude 10-year dementia risk by modifiable risk factor among non-frail, pre-frail, and frail participants.

Risk factors		Overall (N=381,419)				Non-frail (N=222,740)				Pre-frail (N=145,663)				Frail (N=13,016)			
		Size	Cases (Risk)	Difference	P value	Size	Cases (Risk)	Difference	P value	Size	Cases (Risk)	Difference	P value	Size	Cases (Risk)	Difference	P value
	Total	381,419	4,015 (1.05%)			222,740	1,688 (0.76%)			145,663	1,949 (1.34%)			13,016	378 (2.90%)		
Low education	Yes	262,470	3,185 (1.21%)	0.51%	<0.001	145,694	1,263 (0.87%)	0.32%	<0.001	105,813	1,581 (1.49%)	0.57%	<0.001	10,963	341 (3.11%)	1.31%	0.001
	No	118,949	830 (0.70%)			77,046	425 (0.55%)			39,850	368 (0.92%)			2,053	37 (1.80%)		
Physical inactivity	Yes	254,635	2,823 (1.11%)	0.17%	<0.001	137,308	1,025 (0.75%)	-0.03%	0.43	105,101	1,437 (1.37%)	0.11%	0.12	12,226	361 (2.95%)	0.80%	0.19
	No	126,784	1,192 (0.94%)			85,432	663 (0.78%)			40,562	512 (1.26%)			790	17 (2.15%)		
Smoking	Yes	39,659	466 (1.18%)	0.14%	<0.012	20,070	167 (0.83%)	0.08%	0.20	17,086	239 (1.40%)	0.07%	0.46	2,503	60 (2.40%)	-0.62%	0.09
	No	341,760	3,549 (1.04%)			202,670	1,521 (0.75%)			128,577	1,710 (1.33%)			10,513	318 (3.02%)		
Central obesity	Yes	192,026	2,547 (1.33%)	0.55%	<0.001	103,061	966 (0.60%)	-0.34%	<0.001	80,136	1,280 (1.60%)	0.58%	<0.001	8,829	301 (3.41%)	1.57%	<0.001
	No	189,393	1,468 (0.78%)			119,679	722 (0.94%)			65,527	669 (1.02%)			4,187	77 (1.84%)		
Social isolation	Yes	97,054	1,157 (1.19%)	0.18%	<0.001	55,033	443 (0.80%)	0.06%	0.14	38,436	594 (1.55%)	0.29%	<0.001	3,585	120 (3.35%)	0.61%	0.06
	No	284,365	2,858 (1.01%)			167,707	1,245 (0.74%)			107,227	1,355 (1.26%)			9,431	258 (2.74%)		
Hearing impairment	Yes	160,856	2,149 (1.34%)	0.49%	<0.001	88,097	851 (0.97%)	0.35%	<0.001	65,488	1,051 (1.60%)	0.48%	<0.001	7,271	247 (3.40%)	1.12%	<0.001
	No	220,563	1,866 (0.85%)			134,643	837 (0.62%)			80,175	898 (1.12%)			5,745	131 (2.28%)		
Depression	Yes	160,660	1,812 (1.13%)	0.13%	<0.001	79,946	618 (0.77%)	0.02%	0.54	71,855	951 (1.32%)	-0.03%	0.63	8,859	243 (2.74%)	-0.51%	0.11

	No	220,759	2,203 (1.00%)			142,794	1,070 (0.75%)			73,808	998 (1.35%)			4,157	135 (3.25%)		
Hypertension	Yes	117,284	1,994 (1.70%)	0.93%	<0.001	57,491	703 (1.22%)	0.66%	<0.001	52,703	1,037 (1.97%)	0.99%	<0.001	7,090	254 (3.58%)	1.49%	<0.001
	No	264,135	2,021 (0.77%)			165,249	985 (0.60%)			92,960	912 (0.98%)			5,926	124 (2.09%)		
Diabetes	Yes	21,469	573 (2.67%)	1.71%	<0.001	7,181	143 (1.99%)	1.27%	<0.001	11,662	310 (2.66%)	1.44%	<0.001	2,626	120 (4.57%)	2.09%	<0.001
	No	359,950	3,442 (0.96%)			215,559	1,545 (0.72%)			134,001	1,639 (1.22%)			10,390	258 (2.48%)		
Excessive alcohol use	Yes	185,804	1,679 (0.90%)	-0.29%	<0.001	118,494	782 (0.66%)	-0.21%	<0.001	63,650	797 (1.25%)	-0.15%	0.01	3,660	100 (2.73%)	-0.24%	0.50
	No	195,615	2,336 (1.19%)			104,246	906 (0.87%)			82,013	1,152 (1.40%)			9,356	278 (2.97%)		
High NO ₂ exposure	Yes	282,629	3,146 (1.11%)	0.23%	<0.001	159,740	1,248 (0.78%)	0.08%	0.04	111,908	1,568 (1.40%)	0.27%	<0.001	10,981	330 (3.01%)	0.65%	0.11
	No	98,790	869 (0.88%)			63,000	440 (0.70%)			33,755	381 (1.13%)			2,035	48 (2.36%)		
High PM _{2.5} exposure	Yes	284,671	3,123 (1.10%)	0.18%	<0.001	161,527	1,256 (0.78%)	0.07%	0.08	112,267	1,543 (1.22%)	-0.15%	0.03	10,877	324 (2.98%)	0.46%	0.25
	No	96,748	892 (0.92%)			61,213	432 (0.71%)			33,396	406 (1.37%)			2,139	54 (2.52%)		
Traumatic brain injury	Yes	652	19 (2.91%)	1.86%	<0.001	345	7 (2.03%)	1.27%	0.006	267	6 (2.25%)	0.91%	0.20	40	6 (15.00%)	12.13%	<0.001
	No	380,767	3996 (1.05%)			222,395	1,681 (0.76%)			145,396	1,943 (1.34%)			12,976	372 (2.87%)		

Table 3. Adjusted association of modifiable risk factors with 10-year dementia risk by frailty.

Modifiable risk factors	Non-frail (N=222,740)		Pre-frail (N=145,663)		Frail (N=13,016)	
	OR (95% CI) *	P value	OR (95% CI)	P value	OR (95% CI)	P value
Low education	1.11 (0.99, 1.24)	0.08	1.23 (1.09, 1.39)	0.001	1.42 (0.98, 2.06)	0.07
Physical inactivity	1.04 (0.94, 1.15)	0.45	1.12 (1.01, 1.24)	0.04	1.58 (0.94, 2.65)	0.09
Smoking	1.37 (1.16, 1.62)	<0.001	1.24 (1.07, 1.43)	0.004	0.97 (0.72, 1.30)	0.82
Central obesity	1.02 (0.91, 1.14)	0.73	0.95 (0.85, 1.06)	0.34	1.24 (0.94, 1.65)	0.13
Social isolation	1.01 (0.90, 1.13)	0.84	1.14 (1.03, 1.26)	0.009	1.12 (0.88, 1.41)	0.35
Hearing impairment	1.14 (1.03, 1.26)	0.01	1.09 (1.00, 1.20)	0.06	1.28 (1.02, 1.61)	0.03
Depression	1.24 (1.11, 1.37)	<0.001	1.27 (1.16, 1.40)	<0.001	1.09 (0.87, 1.37)	0.45
Hypertension	1.18 (1.06, 1.31)	0.002	1.19 (1.08, 1.32)	<0.001	1.08 (0.85, 1.37)	0.55
Diabetes	1.70 (1.41, 2.04)	<0.001	1.40 (1.22, 1.60)	<0.001	1.44 (1.12, 1.86)	0.004
Excessive alcohol use	0.83 (0.75, 0.91)	<0.001	0.94 (0.85, 1.03)	0.20	0.84 (0.65, 1.07)	0.16
High NO ₂ exposure	1.06 (0.91, 1.24)	0.45	1.27 (1.09, 1.49)	0.003	1.25 (0.84, 1.87)	0.28
High PM _{2.5} exposure	1.04 (0.89, 1.21)	0.64	0.94 (0.81, 1.10)	0.425	1.02 (0.70, 1.49)	0.93
Traumatic brain injury	2.94 (1.36, 6.33)	0.006	1.64 (0.72, 3.75)	0.24	9.43 (3.67, 24.21)	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval

*The logistic regression models included age, sex, ethnicity (whites and others), Townsend deprivation index, APOE e4 carrier status, multimorbidity, and cognitive function at baseline.

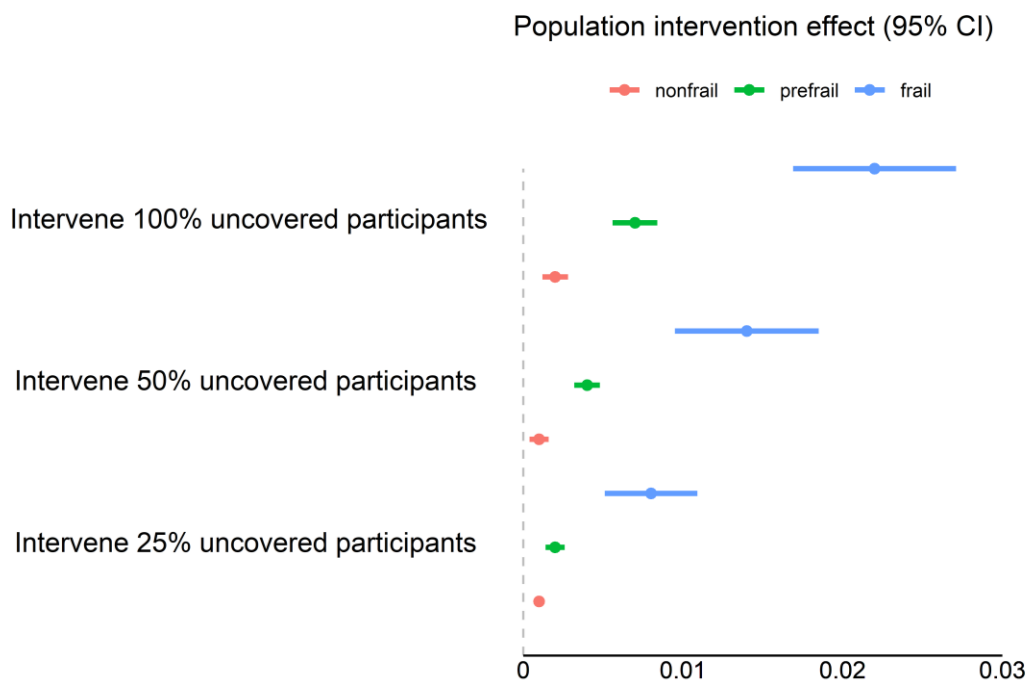


Figure 1. Population intervention effects (PIE) for an intervention of the randomly 25% coverage, randomly 50% coverage and 100% coverage among the uncovered participants. **Note:** Q-models were adjusted for baseline age, sex, ethnicity, Townsend deprivation index, comorbidity index, cognitive function, and APOE e4 carrier status.

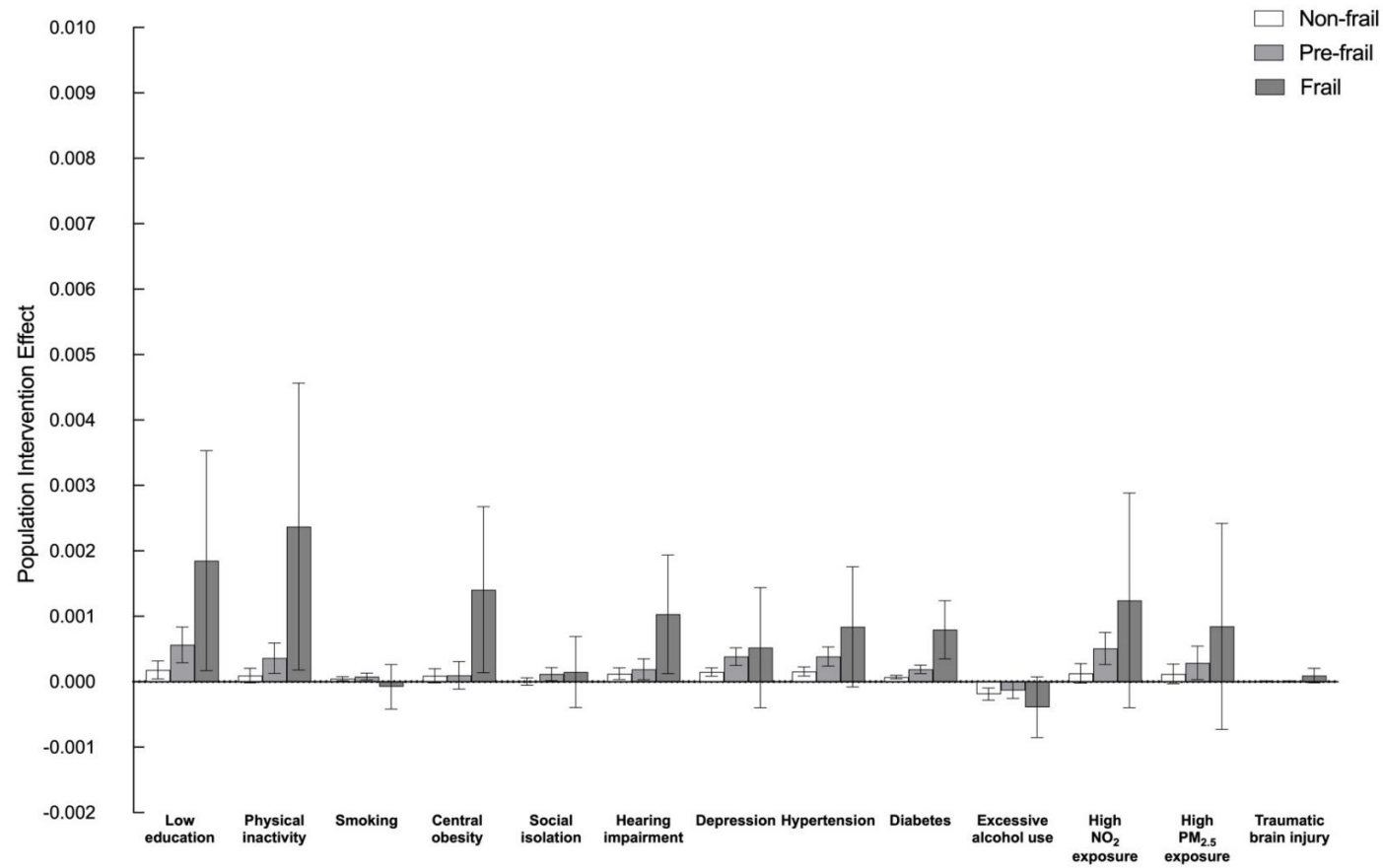


Figure 2A. Population intervention effect (PIE) of each exposure for an intervention of randomly 25% coverage among the non-frail (n=222,740), prefrail (n=145,663), and frail (n=13,016) participants.

Note: Each Q-model was adjusted for baseline age, sex, ethnicity, Townsend deprivation index, comorbidity index, cognitive function, and APOE e4 carrier status.

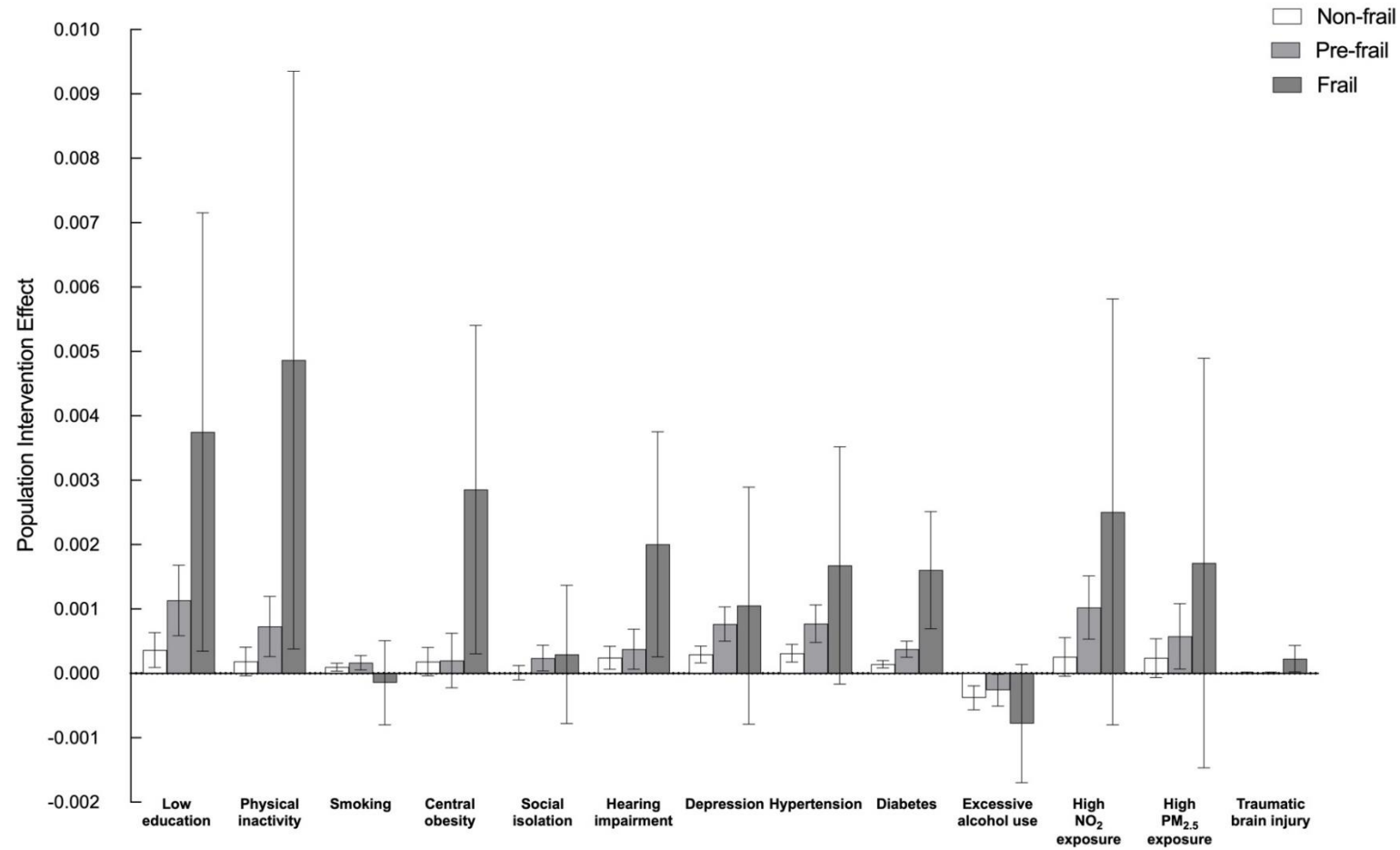


Figure 2B. Population intervention effect (PIE) of each exposure for an intervention of randomly 50% coverage among the non-frail (n=222,740), prefrail (n=145,663), and frail (n=13,016) participants.

Note: Each Q-model was adjusted for baseline age, sex, ethnicity, Townsend deprivation index, comorbidity index, cognitive function, and APOE e4 carrier status.

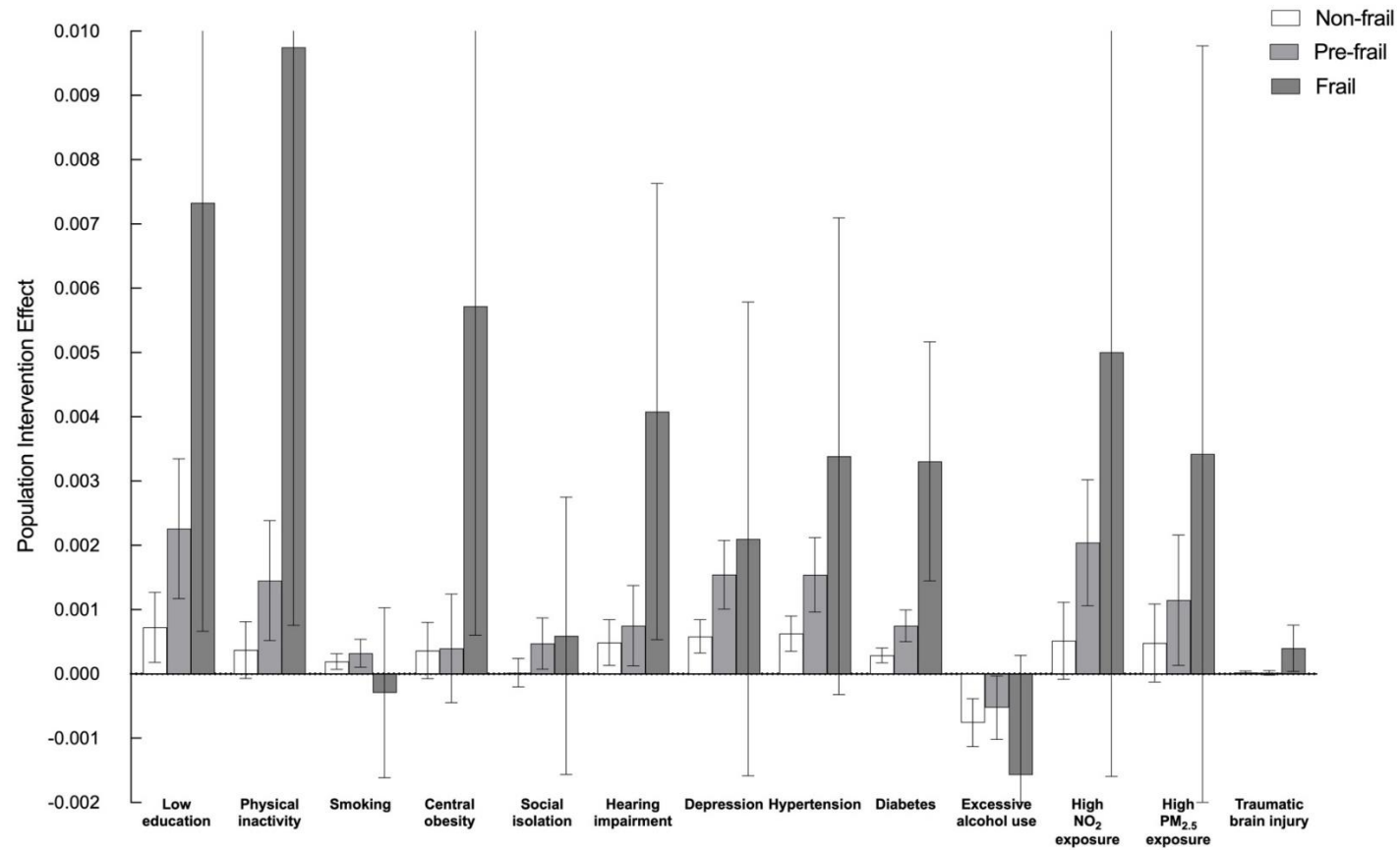


Figure 2C. Population intervention effect (PIE) of each exposure for an intervention of 100% coverage among the non-frail (n=222,740), prefrail (n=145,663), and frail (n=13,016) participants.

Note: Each Q-model was adjusted for baseline age, sex, ethnicity, Townsend deprivation index, comorbidity index, cognitive function, and APOE e4 carrier status.

Table S1. Baseline characteristics of included and excluded participants.

Characteristics	Included N=381,419	Excluded N=120,990	P value*
Age, mean (SD)	56.9 (8.0)	55.3 (8.1)	<0.001
TDI, mean (SD)	-1.4 (3.0)	-1.0 (3.3)	<0.001
Cognitive score, mean (SD)	3.5 (2.2)	3.2 (2.2)	<0.001
Female, n (%)	209,307 (54.9)	64,019 (52.9)	<0.001
Ethnicity, n (%)			<0.001
White	361,391 (95.0)	111,222 (93.2)	
Others	18,893 (5.0)	8,128 (6.8)	
APOE e4 carrier, n (%)	96,664 (25.9)	29,588 (26.0)	<0.001
Comorbidity, n (%)			<0.001
None	328,220 (86.1)	110,138 (91.0)	
One or more conditions	53,199 (13.9)	10,852 (9.0)	
Education, n (%)			<0.001
College or university	118,949 (31.2)	42,180 (38.0)	
Others	262,470 (68.8)	68,681 (62.0)	
Physical inactivity, n (%)	254,635 (66.8)	77,122 (67.4)	<0.001
Smoking, n (%)			<0.001
Never or previous	351,760 (89.0)	107,687 (88.7)	
Current	39,659 (10.4)	13,303 (11.3)	
Central obesity, n (%)	192,026 (50.4)	54,476 (45.9)	<0.001
Social isolation, n (%)	97,054 (25.5)	30,210 (27.9)	<0.001
Hearing impairment, n (%)	160,856 (42.2)	43,894 (37.6)	<0.001
Depression, n (%)	143,360 (37.6)	39,375 (33.0)	<0.001
Hypertension, n (%)	117,284 (30.8)	30,569 (25.3)	<0.001
Diabetes, n (%)	21,469 (5.6)	5,681 (4.7)	<0.001
Excessive alcohol consumption, n (%)	185,804 (48.7)	57,704 (48.3)	<0.001
NO ₂ , mean (SD)	26.5 (7.6)	27.3 (7.6)	<0.001
PM _{2.5} , mean (SD)	10.0 (1.1)	10.0 (1.1)	<0.001
Traumatic brain injury, n (%)	657 (0.2)	140 (0.2)	<0.001

Abbreviations: SD, standard deviation; TDI, Townsend deprivation index.

* Obtained from the t-tests or χ^2 tests.

Table S2. Operational definition of each of five criteria for creating the frailty phenotype score in the UK Biobank.

Criterion	Operational definition in the UK Biobank
Weakness	Measured grip strength (sex and body-mass index adjusted cutoffs taken from Fried and colleagues) ¹
Slowness	Self-reported: “How would you describe your usual walking pace?” (response: slow=1, other=0) ²
Exhaustion	Self-reported: “Over the past two weeks, how often have you felt tired or had little energy?” (response: more than half the days or nearly every day=1, other=0) ²
Physical inactivity	Self-reported: UK Biobank physical activity questionnaire. We classified the responses into: none (no physical activity in the last 4 weeks), low (light DIY activity (e.g., pruning, watering the lawn) only in the past 4 weeks), medium (heavy DIY activity (e.g., weeding, lawn mowing, carpentry and digging), walking for pleasure, or other exercises in the past 4 weeks), and high (strenuous sports in the past 4 weeks) (response: none or light activity with a frequency of once per week or less=1, medium or heavy activity, or light activity more than once per week=0) ³
Shrinking	Self-reported: “Compared with one year ago, has your weight changed?” (response: yes, lost weight=1, other=0) ²

Note: Frailty level was identified by the number of criteria met. Individuals with none were considered “robust/non-frail”; those meeting one or two criteria were considered “pre-frail”; and those with three to five criteria were defined as “frail”.

¹ Definition used in the original description by Fried and colleagues.

² Approximation based on available variables in UK Biobank assessment center data.

³ Definition used in the SHARE adaptation of the frailty phenotype.

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