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Association of cognitive reserve with the risk of dementia in the UK Biobank: role of polygenic factors

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Background

It remains unclear whether cognitive reserve can attenuate dementia risk among people with different genetic predispositions.

Aims

We aimed to examine the association between cognitive reserve and dementia, and further to explore whether and to what extent cognitive reserve may modify the risk effect of genetic factors on dementia.

Method

Within the UK Biobank, 210 631 dementia-free participants aged ≥60 years were followed to detect incident dementia. Dementia was ascertained through medical and death records. A composite cognitive reserve indicator encompassing education, occupation and multiple cognitively loaded activities was created using latent class analysis, categorised as low, moderate and high level. Polygenic risk scores for Alzheimer's disease were constructed to evaluate genetic risk for dementia, categorised by tertiles (high, moderate and low). Data were analysed using Cox models and Laplace regression.

Results

In multi-adjusted Cox models, the hazard ratio (HR) of dementia was 0.66 (95% confidence interval (CI) 0.61–0.70) for high cognitive reserve compared with low cognitive reserve. In Laplace regression, participants with high cognitive reserve developed dementia 1.62 (95% CI 1.35–1.88) years later than those with low cognitive reserve. In stratified analysis by genetic risk, high cognitive reserve was related to more than 30% lower dementia risk compared with low cognitive reserve in each stratum. There was an additive interaction between low cognitive reserve and high genetic risk on dementia (attributable proportion 0.24, 95% CI 0.17–0.31).

Conclusions

High cognitive reserve is associated with reduced risk of dementia and may delay dementia onset. Genetic risk for dementia may be mitigated by high cognitive reserve. Our findings underscore the importance of enhancing cognitive reserve in dementia prevention.

Keywords

Additive interaction; cognitive reserve; dementia; polygenic risk score; UK Biobank.

Background

As the global population ages, the number of people with dementia is rising. It is estimated that approximately 78 million people worldwide will have dementia in 2030.[1] Yet the age-specific incidence of dementia has been on a notably downward trend in some developed Western countries,[2] providing hope that certain intervention strategies to prevent dementia are feasible. Primary prevention, such as limiting exposure to risk factors and building up cognitive reserve in advance, is considered to have the largest effect on the reduction of dementia occurrence in later life.[3]

The concept of cognitive reserve is proposed to account for individual differences in cognitive functioning in the face of brain ageing and damage.[4] More specifically, people with high levels of cognitive reserve are at a decreased risk of cognitive disorders than those with lower cognitive reserve. At a practical level, studies generally use certain proxies to represent cognitive reserve, with education level as the most straightforward and common proxy measure.[5] Moreover, reviews of epidemiological studies have indicated that higher socioeconomic status and more active engagement in social and mental activities may contribute to reduced dementia risk through enhancement of cognitive reserve.[5,6] Cognitive reserve is a dynamic construct that develops from a wide range of experiences over the life course and thus, multiple reserve-enhancing factors need to be considered to sufficiently capture their interplay and accumulation.[4]

In addition to cognitive reserve, genetic background plays an important role in the development of dementia.[7] The ε4 allele of the apolipoprotein E (*APOE*) gene is regarded as a strong genetic risk factor for Alzheimer's disease in late life.[7] A growing body of genome-wide association studies has unveiled additional genetic loci related to the risk of dementia and Alzheimer's disease.[8,9] Polygenic risk scores (PRSs) combining multiple information scattered across genetic loci could provide a quantitative measure of cumulative genetic Alzheimer's disease risk and predict the occurrence of dementia.[9] Although heredity is immutable, it is accepted that the impact of genetic factors can be modified by acquired factors.[9,10] Our previous study has also detected a significant interaction between education level or a composite cognitive reserve indicator and the *APOE* ε4 allele haplotype on dementia risk in Swedish older adults.[11,12] Nevertheless, the contribution of cognitive reserve to polygenic inheritance-related dementia risk is not well understood, and further investigation may provide insights into more effective prediction and targeted prevention strategies.

Aims

We hypothesised that a high level of cognitive reserve is related to lower dementia risk and may attenuate genetic risk for dementia.

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In this community-based longitudinal study from the UK Biobank, we aimed to verify this hypothesis by:

(a) examining the associations between the lifelong cognitive reserve indicator and the risk of all-cause and different subtypes of dementia later in life;
(b) exploring whether such associations differ for individuals with different genetic predispositions to dementia; and
(c) assessing the modulating role of cognitive reserve in dementia risk related to genetic predisposition.

Method

Study population

This research was conducted using the UK Biobank resource (Application Number 67048). UK Biobank is a population-based prospective study of over half a million participants aged 37 to 73 years, recruited from 22 sites across the UK. The UK Biobank study received ethical approval from the North West Multi-Centre Research Ethics Committee (21/NW/0157), and all enrolled participants provided informed and written consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Between 2006 to 2010, 502,412 participants completed a series of sociodemographic, physical and medical assessments at baseline. Peripheral blood samples were additionally collected for genotyping and biochemical assays at this baseline visit. We excluded 284 949 individuals < 60 years (because dementia typically occurs later in life), 164 with prevalent dementia, and 6668 missing genetic information at baseline. A total of 210 631 participants remained for the current study (Supplementary Figure 1 available at https://doi.org/10.1192/bjp.2024.13).

Assessment of cognitive reserve-related factors

Education level, occupational attainment, time spent watching television (TV), confiding in others, social connection and leisure activity engagement were considered proxies of cognitive reserve in the current study. The information on these variables was obtained by participants' self-reports at baseline. If a category in the six aforementioned variables occurred with a frequency of <10%, it was merged with the closest category.

Education level was operationalised as the number of years of regular school and classified as (a) no educational qualifications; (b) Certificate of Secondary Education, O levels/General Certificate of Secondary Education, A levels/AS levels or equivalent; (c) other professional qualifications; (d) National Vocational Qualification, Higher National Diploma, Higher National Certificate or equivalent; or (e) college/university degree.

Occupational attainment was assessed from participants' self-reported employment status and job titles. Each job title was matched to a four-digit job code derived from the Standard Occupational Classification 2000 system, which was developed by the UK Office of National Statistics. Each job code was further categorised according to the Socio-Economic Classification (SEC) system. SEC is coded as an ordinal variable ranging from 1 to 7, with lower values reflecting occupations with more required skills and training.[13] Occupational attainment was therefore categorised as follows: (a) unemployed or routine occupations (SEC 7); (b) small employers and own account workers, lower supervisory and technical occupations, semi-routine occupations (SEC 4–6); (c) intermediate occupations (SEC 3); (d) lower managerial and professional occupations (SEC 2); or (e) higher professional occupations (SEC 1.2) or large employers and higher managerial occupations (SEC 1.1).

Time spent watching TV was assessed based on self-reported total h of daily TV watching and quartiled as (a) ≥4, (b) 3–3.9, (c) 2–2.9, or (d) <2 h.

Frequency of confiding was determined based on how often participants reported confiding in someone close to them, defined as (a) never or almost never, (b) about once a month or less, (c) 1–4 times a week, or (d) almost daily.

Frequency of social connection was measured by asking participants how often they made or received visits with friends or family, classified as (a) no friends/family outside household or about once a month or less, (b) about once a week, (c) 2–4 times a week, or (d) almost daily.

Leisure activities included involvement in a sports club or gym, pub or social club, religious group, adult education class or other group activity. Participants were asked to select which activities they attended at least once a week. The variety of leisure activity engagement was defined as the total number of activities selected, classified as (a) 0, (b) 1, or (c) 2–5.

Assessment of PRS

DNA was extracted from blood samples collected at baseline and genotyped using the UK Biobank Lung Exome Variant Evaluation (UK BiLEVE) Axiom Array or the Affymetrix UK Biobank Axion Array, which respectively cover 807 411 and 825 927 markers across the whole genome.[14] Detailed information on the array content and quality control pipeline is available elsewhere.[14] From these data, a standard PRS reflecting Alzheimer's disease-related genetic risk was constructed. The calculation of this risk score – which has shown high predictive performance for incident Alzheimer's disease and all-cause dementia, comparable with that of other well-established PRSs – has been previously described in detail.[15] Briefly, Alzheimer's disease-related single nucleotide polymorphisms were selected through meta-analysis of multiple external genome-wide association studies. Participants' number of Alzheimer's disease-related alleles was summed after weighing for the strength of each allele's association with Alzheimer's disease, and then *z*-standardised to derive a risk score. This score was tertiled to yield three categories of genetic risk: low ($n = 70\,143$), moderate ($n = 70\,350$) and high ($n = 70\,138$).

Identification of dementia

Dementia was ascertained based on information from self-reports, hospital in-patient records and death records. The hospital in-patient records contain data on diagnoses of diseases from the Hospital Episode Statistics for England, the Scottish Morbidity Record data for Scotland and the Patient Episode Database for Wales. The death register records the causes of death provided by the National Health Service Digital for England and Wales and the Information Services Division for Scotland.

Diseases were diagnosed and coded based on the International Classification of Disease versions 9 (ICD-9) and 10 (ICD-10). The following ICD codes were used to identify dementia cases: ICD-9, 290.2, 290.3, 290.4, 291.2, 294.1, 331.0, 331.1, 331.2, 331.5; ICD-10, F00–03, F05.1, G30, G31.1, G31.8. For the current analyses, the algorithmically defined all-cause dementia, Alzheimer's disease and vascular dementia (VaD) outcomes (Field ID: 42018–42023) were used.

Covariates

A broad range of potential confounders were considered and collected at baseline, including age, gender, ethnicity, smoking status, alcohol consumption, physical activity, body mass index (BMI), hypertension, diabetes, heart disease, stroke, and *APOE* ε4 allele carrier status. They are described in detail in Supplementary Method 1.

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Statistical analysis

Latent class analysis (LCA) was used to create a comprehensive cognitive reserve indicator, which can identify hidden clusters by grouping multiple observed variables (i.e. cognitive reserve-related factors) into a latent variable with mutually exclusive latent classes (i.e. the cognitive reserve indicator). To find the optimal fitting model for the current data, LCA models with one to six latent classes were conducted. G^2 statistics and Bayesian information criterion were used for model selection, with lower values indicating a more reasonable model. The mean posterior probabilities in these models were examined to assess the uncertainty of posterior classification, with a value of ≥0.7 indicating an acceptable uncertainty.

Baseline characteristics of participants were summarised across different cognitive reserve classes, and differences were tested by using one-way analysis of variance for continuous variables or chi-square test for categorical variables.

Cox proportional hazard regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for the association of different levels of cognitive reserve and genetic risk with dementia. Follow-up time was calculated as the time from baseline to the earliest occurrence of dementia, death or the end of follow-up (31 January 2022), whichever occurred first. The proportional hazards assumptions for the Cox models were tested using the Schoenfeld residuals technique; no violation of proportionality was observed.

Laplace regression, as a complement to Cox models, was used to estimate the absolute difference in the median time until dementia onset according to different levels of cognitive reserve. Given that <10% of participants experienced the outcome, we assessed differences in time (in years) by which the first 10% of participants developed dementia. Furthermore, stratified analyses by genetic risk category were performed to ascertain the difference in cognitive reserve–dementia association between participants with different genetic predispositions. Multiplicative interaction was examined by incorporating the two factors (i.e. the cognitive reserve indicator and genetic risk) and their cross-product term in the same models.

To assess the joint effect of cognitive reserve and genetic risk on dementia, we created a variable with nine categories according to the combination of the two factors and estimated the corresponding HRs of dementia (high cognitive reserve plus low genetic risk as reference group). Additive interaction was tested by computing the relative excess risk due to interaction (RERI), the attributable proportion (AP) and the synergy index (S), with Bonferroni correction for nine simultaneous tests (Supplementary Method 2). All analyses were first adjusted for age, gender and ethnicity and then further adjusted for smoking status, alcohol consumption, physical activity, BMI, hypertension, diabetes, heart disease and stroke, as well as the cognitive reserve indicator and genetic risk (when appropriate). Missing values for cognitive reserve-related factors and covariates were imputed using multiple imputation by chained equations (Supplementary Method 3).

All *P*-values were two-tailed, and those <0.05 were considered statistically significant. Analyses were performed using SAS 9.4 (SAS institute, Cary, NC) and Stata SE 15.0 (StataCorp, College Station, TX, USA).

Results

Generation of cognitive reserve indicator

In LCA models, G^2 statistics and Bayesian information criterion decreased as the number of latent classes grew from one to six. However, some of the mean posterior probabilities were <0.70 when the number of latent classes exceeded three (Supplementary Table 1). As a result, the three-latent-class model was identified as having the best balance between model selection and the uncertainty of posterior classification.

Latent class 1 ('high cognitive reserve') was characterised by favourable levels of cognitive reserve-related factors in general, specifically, with higher education, higher occupational attainment, less time spent watching TV, more frequency of confiding and a wider variety of leisure activity engagement. Latent class 2 ('moderate cognitive reserve') was characterised by moderately favourable levels of all cognitive reserve-related factors. Latent class 3 ('low cognitive reserve') was characterised by more frequency of social connection but less favourable levels of other cognitive reserve-related factors (Fig. 1 and Supplementary Table 2).

Of all the participants, 63 826 (30.30%) had high cognitive reserve, 89 857 (42.66%) had moderate cognitive reserve and 56 948 (27.04%) had low cognitive reserve.

Characteristics of the study population

At baseline, the mean age was 64.14 (s.d. = 2.85 years, ranging from 60 to 73 years), and 52.60% were female among the 210 631 participants. Compared with participants with moderate or high cognitive reserve, those with low cognitive reserve were more likely to be older, White, current or previous smokers, previous or non-drinkers and to have inactive physical activity, higher BMI, higher genetic risk for dementia, and a history of hypertension, diabetes, heart disease and/or stroke (Table 1).

Association of cognitive reserve and genetic risk with dementia

During the follow-up (median: 12.74 years, interquartile range: 11.93 to 13.50 years), 6371 participants developed dementia, including 2767 with Alzheimer's disease and 1490 with VaD.

In multi-adjusted Cox models, the HRs (95% CIs) of dementia were 0.79 (95% CI 0.75–0.84) for moderate cognitive reserve and 0.66 (95% CI 0.61–0.70) for high cognitive reserve in comparison with low cognitive reserve. Furthermore, both moderate and high cognitive reserve were associated with reduced risk of Alzheimer's disease and VaD (Table 2).

In multi-adjusted Laplace regression, participants with moderate or high cognitive reserve developed dementia 0.88 (10th percentile difference, 95% CI 0.65–1.10) years later or 1.62 (10th percentile difference, 95% CI 1.35–1.88) years later, respectively, than those with low cognitive reserve. The onsets of Alzheimer's disease and VaD were also delayed by 0.82 to 2.16 years by moderate or high cognitive reserve (Supplementary Table 3).

In terms of genetic risk, when compared with participants with low genetic risk, those with moderate (HR = 1.37, 95% CI: 1.27–1.48) and high (HR = 3.32, 95% CI: 3.11–3.55) genetic risk had higher dementia incidence. In addition, the PRS for Alzheimer's disease increased not only Alzheimer's disease risk but also VaD risk (Table 2). Similar results were observed in the basic-adjusted models (Supplementary Table 4).

Association of cognitive reserve with dementia according to different levels of genetic risk

Further analyses stratified by genetic risk category (low cognitive reserve as the reference group) showed that high cognitive reserve was associated with decreased risk of incident all-cause dementia, Alzheimer's disease and VaD across all three genetic risk groups (Fig. 2(a) and Supplementary Table 5). For instance, even among participants at high genetic risk, those with high cognitive reserve had reduced risk of all-cause dementia (HR = 0.65, 95% CI 0.59–0.71), Alzheimer's disease (HR = 0.61, 95% CI 0.54–0.69) and

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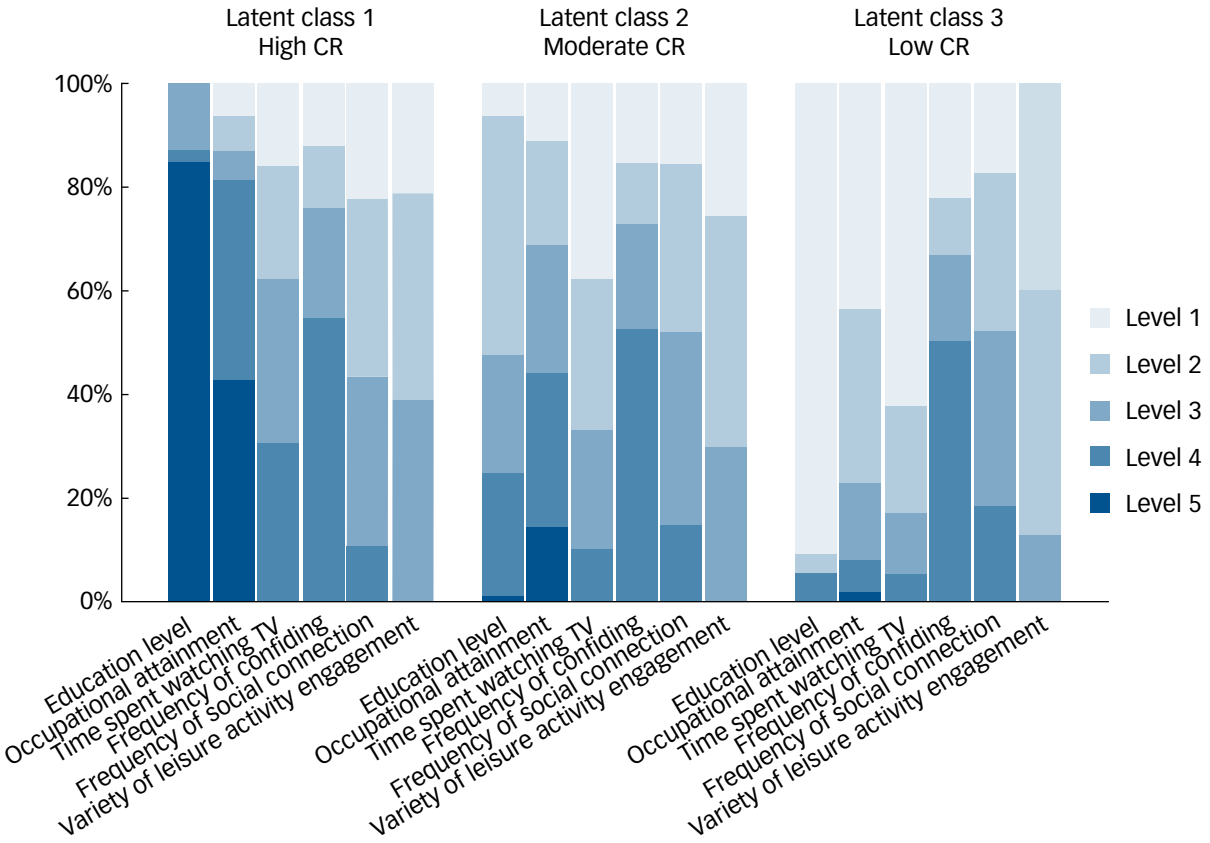

Fig. 1 Distribution of levels of cognitive reserve-related factors in three latent classes. Darker colours indicate more favourable and lighter colours indicate less favourable levels of each cognitive reserve-related factor. CR, cognitive reserve; TV, television.

VaD (HR = 0.51, 95% CI 0.42–0.63). However, there was no significant relationship between moderate cognitive reserve and Alzheimer's disease or VaD among those with low genetic risk. No indication of multiplicative interaction between cognitive reserve and genetic risk on all-cause dementia ($P = 0.895$), Alzheimer's disease ($P = 0.380$) or VaD ($P = 0.988$) was detected.

Table 1 Baseline characteristics of the study population by different levels of cognitive reserve

Characteristics	Cognitive reserve			*P*
	Low (*n* = 56 948)	Moderate (*n* = 89 857)	High (*n* = 63 826)	
Age, years, mean (s.d.)	64.57 (2.86)	64.06 (2.84)	63.85 (2.82)	<0.001
Female, *n* (%)	31 007 (54.45)	49 485 (55.07)	30 291 (47.46)	<0.001
Ethnicity, White, *n* (%)	54 067 (94.94)	84 831 (94.41)	58 036 (90.93)	<0.001
Smoking status, *n* (%)				<0.001
Never	25 062 (44.01)	44 692 (49.74)	35 472 (55.58)	
Previous	24 919 (43.76)	38 290 (42.61)	24 787 (38.84)	
Current	6967 (12.23)	6875 (7.65)	3567 (5.59)	
Alcohol consumption, *n* (%)				<0.001
Never	3872 (6.80)	3975 (4.42)	2204 (3.45)	
Previous	3380 (5.94)	2802 (3.12)	1824 (2.86)	
Current	49 696 (87.27)	83 080 (92.46)	59 798 (93.69)	
Physical activity, *n* (%)				<0.001
Inactive	8677 (15.24)	13 218 (14.71)	9570 (14.99)	
Moderate	24 400 (42.85)	42 468 (47.26)	33 712 (52.82)	
Active	23 871 (41.92)	34 171 (38.03)	20 544 (32.19)	
Body mass index, kg/m^2, mean (s.d.)	28.45 (4.79)	27.66 (4.51)	26.73 (4.19)	<0.001
Hypertension, *n* (%)	26 842 (47.13)	36 351 (40.45)	22 566 (35.36)	<0.001
Diabetes, *n* (%)	5650 (9.92)	6275 (6.98)	3563 (5.58)	<0.001
Heart disease, *n* (%)	7518 (13.20)	7737 (8.61)	4172 (6.54)	<0.001
Stroke, *n* (%)	1919 (3.37)	1968 (2.19)	1047 (1.64)	<0.001
Polygenic risk score, mean (s.d.)	0.05 (0.99)	0.04 (0.99)	0.04 (0.99)	0.013
Genetic risk, *n* (%)				0.032
Low	18 751 (32.93)	30 142 (33.54)	21 250 (33.29)	
Moderate	19 025 (33.41)	29 825 (33.19)	21 500 (33.69)	
High	19 172 (33.67)	29 890 (33.26)	21 076 (33.02)	

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Table 2 Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia in relation to cognitive reserve and genetic risk: results from Cox models ($n = 210\,631$)

		All-cause dementia		Alzheimer's disease		Vascular dementia	
Exposures	Participants, *n*	Incident cases, *n*	Multi-adjusted HR (95% CI)	Incident cases, *n*	Multi-adjusted HR (95% CI)	Incident cases, *n*	Multi-adjusted HR (95% CI)
Cognitive reserve							
Low	56 948	2381	1.00 (Reference)	1035	1.00 (Reference)	623	1.00 (Reference)
Moderate	89 857	2553	0.79 (0.75–0.84)	1138	0.80 (0.73–0.87)	595	0.76 (0.68–0.86)
High	63 826	1437	0.66 (0.61–0.70)	594	0.61 (0.55–0.68)	272	0.54 (0.47–0.63)
Genetic risk							
Low	70 143	1143	1.00 (Reference)	375	1.00 (Reference)	281	1.00 (Reference)
Moderate	70 350	1563	1.37 (1.27–1.48)	570	1.52 (1.33–1.73)	388	1.38 (1.18–1.61)
High	70 138	3665	3.32 (3.11–3.55)	1822	5.01 (4.47–5.59)	821	3.01 (2.62–3.44)

Models were adjusted for age, gender, ethnicity, smoking status, alcohol consumption, physical activity, body mass index, hypertension, diabetes, heart disease, stroke, cognitive reserve indicator and genetic risk, if applicable.

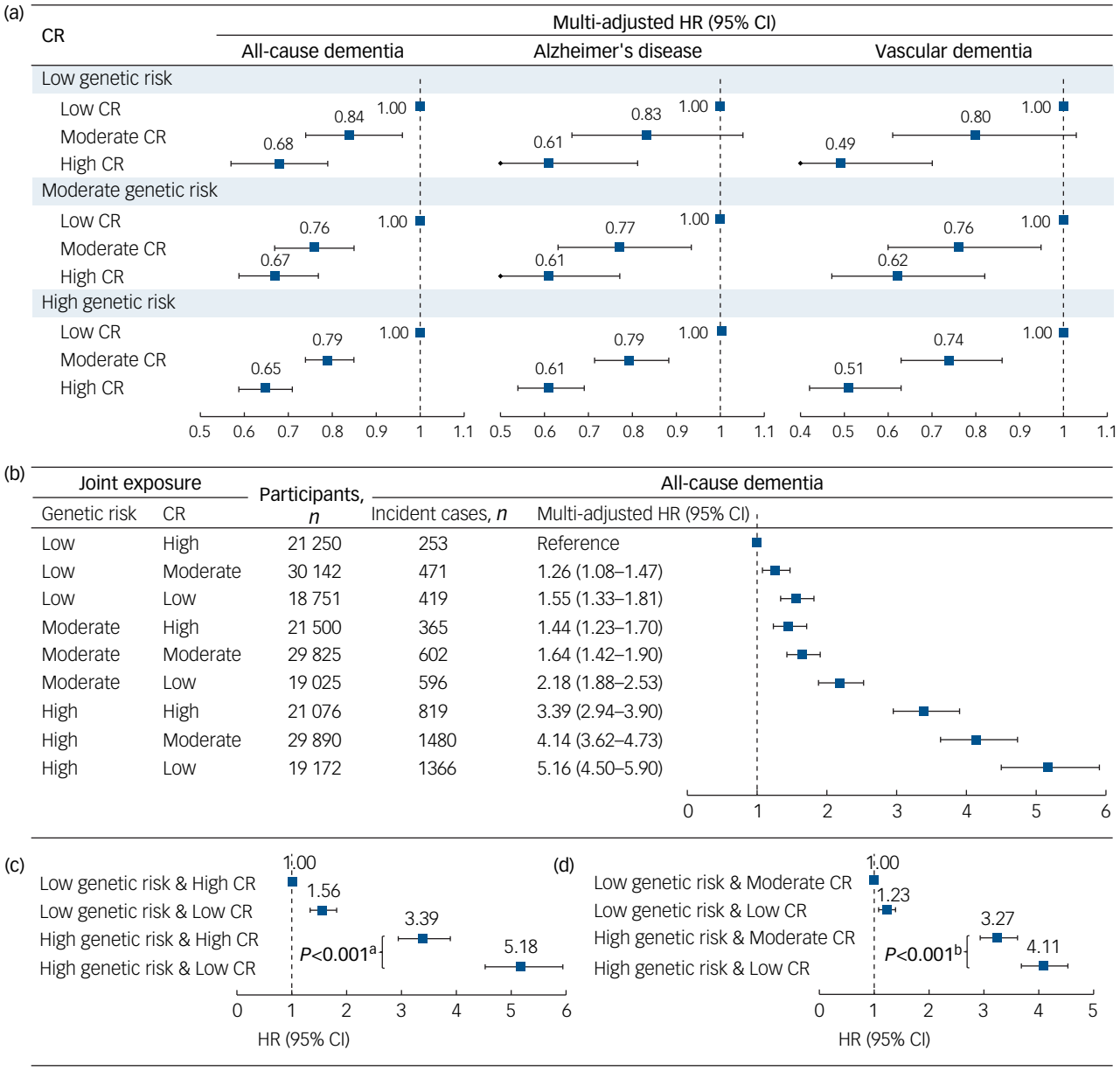

Fig. 2 Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia in relation to (a) cognitive reserve stratified by genetic risk, (b) joint exposures of cognitive reserve and genetic risk, (c) joint exposures of high/low cognitive reserve and low/high genetic risk, and (d) joint exposures of moderate/low cognitive reserve and low/high genetic risk. Models were adjusted for age, gender, ethnicity, smoking status, alcohol consumption, physical activity, body mass index, hypertension, diabetes, heart disease and stroke. [a]A significant difference in HRs between high cognitive reserve combined with high genetic risk and low cognitive reserve combined with high genetic risk. [b]A significant difference in HRs between moderate cognitive reserve combined with high genetic risk and low cognitive reserve combined with high genetic risk. CR, cognitive reserve.

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In addition, results from Laplace regression showed that dementia onset was delayed by 1.38 to 1.73 years by high cognitive reserve in different genetic risk groups (Supplementary Table 6). These results suggest minimal variation in the cognitive reserve–dementia association between individuals with different levels of genetic risk.

Joint effect of cognitive reserve and genetic risk on dementia

In joint effect analyses, the risk of dementia increased monotonically with increasing genetic risk combined with decreasing cognitive reserve (Fig. 2(b) and Supplementary Table 7).

Specifically, compared with individuals with high cognitive reserve plus low genetic risk, those with low cognitive reserve plus low genetic risk (HR = 1.56, 95% CI 1.33–1.83), high cognitive reserve plus high genetic risk (HR = 3.39, 95% CI 2.94–3.90) and low cognitive reserve plus high genetic risk (HR = 5.18, 95% CI 4.52–5.94) had higher dementia risk, with a significant additive interaction (RERI = 1.24, 95% CI 0.84–1.64; AP = 0.24, 95% CI 0.17–0.31; S = 1.42, 95% CI 1.25–1.62; all corrected $P < 0.001$). The difference in HRs between high cognitive reserve plus high genetic risk and low cognitive reserve plus high genetic risk was significant (HR = 0.65, 95% CI 0.60–0.72), indicating that the risk of dementia related to high genetic risk was diminished by 35% by high cognitive reserve (Fig. 2(c)).

In addition, there was a significant additive interaction between moderate/low cognitive reserve and low/high genetic risk (RERI = 0.60, 95% CI 0.29–0.90; AP = 0.14, 95% CI 0.07–0.22; S = 1.24, 95% CI 1.10–1.39; all corrected $P < 0.01$). The difference in HRs between moderate cognitive reserve plus high genetic risk and low cognitive reserve plus high genetic risk was also significant (HR = 0.80, 95% CI 0.74–0.86), indicating that dementia risk related to high genetic risk was diminished by 20% by moderate cognitive reserve (Fig. 2(d)).

Participants with moderate genetic risk were also at proportionally higher dementia risk with a reduction in cognitive reserve level. However, no significant additive interaction between cognitive reserve and low/moderate genetic risk on dementia was detected. We also explored a joint effect of cognitive reserve and *APOE* ε4 allele on dementia and a similar pattern of associations was observed (Supplementary Table 8).

Sensitivity analysis

We performed the following sensitivity analyses: by substituting the overall cognitive reserve indicator with individual cognitive reserve-related factors, reduced risks of dementia with the most compared with the least favourable levels of each factor were observed; HRs ranged from 0.60 to 0.91 (Supplementary Table 9). In addition, the results remained robust in analyses using competing risk models (the Fine–Gray subdistribution hazard model) with death as the competing event (HRs of dementia were 0.81 (95% CI 0.76–0.86) for moderate cognitive reserve and 0.68 (95% CI 0.63–0.73) for high cognitive reserve; Supplementary Table 10) and after excluding incident dementia cases occurring in the first 5 years from baseline ($n = 594$) to reduce the possibility of reverse causality (HRs of dementia were 0.79 (95% CI 0.74–0.84) for moderate cognitive reserve and 0.65 (95% CI 0.60–0.70) for high cognitive reserve; Supplementary Table 11).

Discussion

Main findings

In this community-based longitudinal study from the UK Biobank, we combined multiple factors involving aspects of education, occupation, cognitively passive sedentary behaviour, and social/leisure activities to construct a comprehensive cognitive reserve indicator. We found that:

(a) compared with low cognitive reserve, high cognitive reserve was associated with >30% reduced risk of dementia and delayed dementia onset for about 1.6 years;
(b) the cognitive reserve–dementia association remained significant across all strata of genetic risk; and
(c) there was a synergistic effect of low cognitive reserve and high genetic risk on dementia, where high cognitive reserve attenuated the risk of dementia related to high genetic risk by about a third.

Comparison with previous findings and interpretation of our findings

Accumulating evidence has reported protective effects of single-factor measures of cognitive reserve including higher education,[16] higher occupational class[17] and avoiding watching TV for a long time (regarded as mentally passive sedentary behaviour)[18] against dementia. A single component, however, could not fully reflect and explain the cognitive reserve construct that was influenced by various experiences. Thus, a shift toward more integrated measures has been discussed in the literature. Several studies have combined and averaged multiple proxy indicators to evaluate cognitive reserve;[17,19] however, the relative weighting of each proxy and how to consider the differences in each level within the proxy variables are controversial.

Other studies including our previous work have applied latent variable models that allow for different weights of cognitive reserve-related factors, and shown that a high cognitive reserve score (indexed by education, socioeconomic status, occupation and leisure activities[20] or by education and cognitive and social activities[21]) is related to a reduction in dementia risk. In the present study, we added previously unmeasured proxies, such as screen-based sedentary behaviour and occupational attainment, and we used LCA to construct a comprehensive cognitive reserve indicator. We also took the further step of exploring the associations of cognitive reserve with the risk and onset time of all-cause and specific subtypes of dementia. We found that high-level cognitive reserve was associated with 34% to 46% decreased risk of all-cause dementia, Alzheimer's disease and VaD, as well as a delay in disease onset by over 1.6 years. Our findings indicate that enhancing cognitive reserve through greater exposure to cognitively loaded experiences might be an effective dementia-prevention strategy.

In recent years, the PRS aggregating multiple risk alleles has been applied to quantitatively assess individual genetic predisposition to several complex diseases, including dementia and Alzheimer's disease. Genetic factors are thought to be key drivers of dementia, a notion that is reflected by our finding of a fivefold higher risk for Alzheimer's disease and a threefold higher risk for all-cause dementia and VaD among those with the highest tertile of PRS for Alzheimer's disease. Despite this, the observed cognitive reserve–dementia relationship did not differ by genetic risk, further supporting the protective effect of cognitive reserve against dementia for the entire population regardless of predetermined genetic factors.

Thus far, few prospective studies have reported the joint effect of cognitive reserve-related factors and genetic risk, showing that education,[12] leisure activities[12] and cognitively stimulating activities[11] might modify the impact of the *APOE* ε4 allele on dementia. In our study, we further investigated the interactive effect of the comprehensive proxy measure of cognitive reserve and polygenetic predisposition to dementia (including not just the *APOE* ε4 allele) and found a significant synergistic effect. Specifically, 24% of dementia

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risk could be attributed to the additive interactions between low cognitive reserve and high genetic risk, suggesting that this combined effect was greater than the sum of the two individual effects. Moreover, high cognitive reserve might mitigate dementia risk related to high genetic predisposition by about a third. These findings have important public health implications, because interventions designed to build up cognitive reserve will be more effective when targeted at a subpopulation who face higher dementia risk, namely those with the highest genetic predisposition.

Several underlying mechanisms have been proposed to explain the cognitive reserve–dementia association. In our previous work, we did not find a neuroprotective effect of enhanced cognitive reserve against Alzheimer's disease or vascular pathology among older adults,[21] supporting the cognitive reserve hypothesis that cognitive reserve might not affect age-related brain changes or pathologies directly but represent other pathways to compensate for or cope with these changes,[4,22] such as enhancing brain network efficiency[22] and contributing to neurotrophic effects in the mid-prefrontal lobe and greater neuronal density.[23] In addition, research using mouse models suggests that environmental enrichment, defined as the generation of novelty and complexity in housing conditions that strengthens cognitive stimulation[24] is linked to neural plasticity in brain regions critically involved in cognitive functioning, including the growth of new neurons and synapses and the upregulation of brain-derived neurotrophic factor.[24]

Strengths and limitations

Strengths of our study include the use of LCA to structure a composite cognitive reserve indicator with a good overall fit, which captures multiple cognitive reserve-related factors and their complex interplays simultaneously. Additionally, genetic predisposition to dementia based on the PRS is taken into consideration, enabling us to precisely determine the effects of cognitive reserve on individuals with varying levels of disease predisposition.

Limitations of the study should also be acknowledged. First, cognitive reserve is a hypothetical and theoretical construct. Currently, there is no standard method for assessing cognitive reserve, and thus different studies have used different measures of cognitive reserve based on data availability. Additionally, we did not include cognitive performance in our measurement of cognitive reserve because nearly two-thirds of participants did not participate in the comprehensive cognitive assessments, and because cognitive performance is considered more likely to be a reflection of cognitive reserve rather than a driver of or contributor to cognitive reserve. Nevertheless, taking advantage of the comprehensive data available in the UK Biobank, we attempted to construct a proxy measure of cognitive reserve covering multiple sociobehavioural factors that could potentially contribute to cognitive reserve accumulation.[4,5,20,21] Further studies are warranted to develop well-defined measures for cognitive reserve.

Second, people with incident dementia cases during follow-up were identified using register-based data but not detailed neuropsychological assessments. Thus, some people with dementia may have escaped detection. It is not clear whether this misclassification is differential across the exposure groups.

Third, diagnoses of Alzheimer's disease and VaD were not ascertained through brain biopsy or post-mortem, which may have led to misclassification of the dementia subtypes, particularly considering the high occurrence of mixed Alzheimer's disease and VaD pathological changes among older adults.[25]

Fourth, because the onset of dementia commonly precedes clinical diagnosis and its exact date is difficult to estimate, the observed cognitive reserve–dementia association is subject to reverse causality. However, the exclusion of people identified with dementia within 5 years after baseline did not substantially alter our results. Finally, this sample was restricted to older volunteers who were relatively highly educated and primarily of White European ancestry, so caution is needed when generalising our findings to other populations.

Implications

In conclusion, this study demonstrates that a high level of cognitive reserve is associated with reduced dementia risk and may postpone the onset of dementia. Our findings also provide evidence that higher cognitive reserve may buffer the deleterious effect of predisposing genetic factors on dementia, and thus highlight the importance of enhancing cognitive reserve for the prevention of dementia, especially among those at high genetic risk.

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Supplementary material

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Data availability

Access to UK Biobank data can be requested through a standard data access procedure. Requests to access these data-sets should be directed to http://www.ukbiobank.ac.uk/register-apply. The analytic codes supporting the findings are available from the corresponding author upon reasonable request. The materials supporting the findings are available from the corresponding author upon reasonable request.

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Author contribution

W.Y. and W.X. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. W.X. and W.Y. contributed to the conception and design of the study. W.Y. conducted the statistical analyses with support from J.W., performed the literature search and drafted the manuscript. J.W., A.D., M.M.D., X.Q., D.A.B. and W.X. reviewed and edited the manuscript. All authors critically revised the manuscript for important intellectual content. All authors made a significant contribution to finalising the manuscript and approved the final version for publication.

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Declaration of interest

None.

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