**Supplementary material**

This supplementary material was supporting the results for the manuscript titled *Association of cognitive reserve with the risk of dementia in the UK Biobank: Role of polygenic factors* by Yang et al.

**Contents**

|  |  |
| --- | --- |
| Supplementary Method 1 Details on assessments of age, gender, ethnicity, smoking status, alcohol consumption, physical activity, body mass index, hypertension, diabetes, heart disease, stroke, and apolipoprotein E ε4 allele carrier status | Page 2 |
| Supplementary Method 2 Details on joint effect analyses and tests of additive interaction | Page 3 |
| Supplementary Method 3 Details on missing data and multiple imputation method | Page 4 |
| Supplementary Table 1 *G*2 statistics, Bayesian information criterion, and mean posterior probabilities in models with different numbers of latent classes | Page 5 |
| Supplementary Table 2 Distribution characteristics of levels of cognitive reserve-related variables in three latent classes (n=210,631) | Page 6 |
| Supplementary Table 3 The 10th percentile differences (PDs) and 95% confidence intervals in time (years) to dementia onset in relation to cognitive reserve: results from Laplace regression (n=210,631) | Page 7 |
| Supplementary Table 4 Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia in relation to cognitive reserve and genetic risk in basic-adjusted Cox models (n=210,631) | Page 8 |
| Supplementary Table 5 Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia in relation to cognitive reserve (CR), stratified according to genetic risk category (n=210,631) | Page 9 |
| Supplementary Table 6 The 10th percentile differences (PDs) and 95% confidence intervals in time (years) to dementia onset in relation to cognitive reserve (CR), stratified according to genetic risk category (n=210,631) | Page 10 |
| Supplementary Table 7 Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia in relation to joint exposure of genetic risk and cognitive reserve (n=210,631) | Page 11 |
| Supplementary Table 8 Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia in relation to joint exposure of apolipoprotein E ε4 allele and cognitive reserve | Page 12 |
| Supplementary Table 9 Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia in relation to each cognitive reserve-related factor (n=210,631) | Page 13 |
| Supplementary Table 10 Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia in relation to cognitive reserve using competing risk models (n=210,631) | Page 14 |
| Supplementary Table 11 Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia at least 5 years after baseline in relation to cognitive reserve (n=210,037) | Page 15 |
| Supplementary Figure Flowchart of the study population | Page 16 |

**Supplementary Method 1 Details on assessments of age, gender, ethnicity, smoking status, alcohol consumption, physical activity, body mass index, hypertension, diabetes, heart disease, stroke, and apolipoprotein E ε4 allele carrier status**

At baseline, information on age, gender, ethnicity, smoking status, alcohol consumption, and physical activity was self-reported through computerized touch-screen questionnaires. Ethnicity was dichotomized as white versus non-white (including mixed, Asian or Asian British, black or black British, Chinese, or other ethnic groups). Cigarette smoking status was grouped as never, previous, or current smoking. Alcohol consumption was categorized as never, previous, or current drinking. Physical activity was measured in terms of metabolic equivalents (MET) per week using the International Physical Activity Questionnaire short form and classified as inactive (<600 MET-min/week), moderate (600 to <3000 MET-min/week), or active (≥3000 MET-min/week) [1]. Height and weight were measured during the baseline examination after participants removed their shoes and heavy outer clothing. Body mass index (kg/m2) was calculated as weight (kg) divided by the square of height (m). Hypertension was identified based on systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, self-reported history of hypertension, use of antihypertensive drugs, or medical records. Diabetes was considered if the presence of hemoglobin A1c ≥6.5%, fasting plasma glucose ≥126 mg/dl, self-reported history of diabetes, use of glucose-lowering medications, or medical records. Heart disease, including myocardial infarction, angina, atrial fibrillation, and heart failure, was assessed through medical records and self-reported medical history. Stroke was ascertained through medical records and self-reported medical history. The apolipoprotein E gene was genotyped and dichotomized as carriers or non-carriers of the ε4 allele.

Reference

[1] Chudasama YV, Khunti KK, Zaccardi F, et al. Physical activity, multimorbidity, and life expectancy: a UK Biobank longitudinal study. *BMC Med* 2019;17:108.

**Supplementary Method 2 Details on joint effect analyses and tests of additive interaction**

In joint effect analyses, we created a 9-group variable reflecting the participant’s joint cognitive reserve (CR; high, moderate, or low) and genetic risk (low moderate, or high) status, as follows: 1) low genetic risk & high CR (reference group); 2) low genetic risk & moderate CR; 3) low genetic risk & low CR; 4) moderate genetic risk & high CR; 5) moderate genetic risk & moderate CR; 6) moderate genetic risk & low CR; 7) high genetic risk & high CR; 8) high genetic risk & moderate CR; and 9) high genetic risk & low CR. All corresponding hazard ratios of dementia are reported in **Figure 2(b)** and **Supplementary Table 7.**

Because the test of additive interaction is applicable for the combination of two factors which respectively have two levels (namely a combined categorical variable with 4 categories), we conducted 9 tests of additive interaction using 4 groups at a time. Additive interaction was tested by computing the relative excess risk due to interaction, the attributable proportion, and the synergy index. The *P*-value with respect to these statistics was adjusted with Bonferroni correction (original *P*-value × 9). We only observed significant additive interactions in the combination of groups 1), 3), 7), 9) (**Figure 2(c)**) and the combination of groups 2), 3), 8), 9) (**Figure 2(d)**) tests and reported them in the main text. Results with non-significant additive interaction are not shown.

**Supplementary Method 3 Details on missing data and multiple imputation** **method**

In touch-screen questionnaires, responses corresponding to “Do not know” or “Prefer not to answer” were additionally treated as missing data. For occupation, if participants only indicated that they were retired, their occupational attainment was also treated as missing data. Missing values for cognitive reserve-related factors (education level [1.52%], occupational attainment [19.46%], time spent watching TV [1.10%], confiding [4.01%], social connection [0.78%], and leisure activities [0.45%]) and some of the covariates (ethnicity [0.46%], smoking status [0.61%], alcohol consumption [0.22%], physical activity [21.27%], and body mass index [0.40%]) were imputed using multiple imputation by chained equations with 5 imputations. We performed all analyses with each of the 5 imputed datasets one by one using the same analytic methods and then the estimates were pooled using Rubin’s rules to obtain valid statistical inferences.

Missing values for polygenic risk scores were not imputed. These polygenic risk scores already have missing values of multiple genetic loci imputed, and missing data on polygenic risk scores may indicate a high missing proportion within a certain risk allele and/or a high missing proportion of the variety of risk alleles of interest. Further imputation could lead to unreliable results. Therefore, we excluded individuals missing genetic information at baseline.

**Supplementary Table 1** *G*2 statistics, Bayesian information criterion, and mean posterior probabilities in models with different numbers of latent classes

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Models** | ***G*2** | **Bayesian information criterion** | **Mean posterior probabilities** | | | | | |
| Latent class 1 | Latent class 2 | Latent class 3 | Latent class 4 | Latent class 5 | Latent class 6 |
| One-latent-class model | 107287.98 | 107520.88 | 1.00 | - | - | - | - | - |
| Two-latent-class model | 27738.40 | 28216.46 | 0.90 | 0.90 | - | - | - | - |
| Three-latent-class model | 17814.82 | 18539.04 | 0.83 | 0.85 | 0.76 | - | - | - |
| Four-latent-class model | 13402.51 | 14370.88 | 0.80 | 0.61 | 0.71 | 0.80 | - | - |
| Five-latent-class model | 10658.81 | 11872.34 | 0.79 | 0.68 | 0.65 | 0.64 | 0.59 | - |
| Six-latent-class model | 9268.27 | 10726.96 | 0.58 | 0.53 | 0.73 | 0.66 | 0.61 | 0.61 |

**Supplementary Table 2** Distribution characteristics of levels of cognitive reserve-related variables in three latent classes (n=210,631)

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **Latent classes** | | |
| Latent class 1  (n=63826) | Latent class 2  (n=89857) | Latent class 3  (n=56948) |
| **Education level** |  |  |  |
| No educational qualifications | 0 | 5517 (6.14) | 51684 (90.76) |
| CSEs, O levels/GCSE, A levels/AS levels or equivalent | 0 | 41380 (46.05) | 2090 (3.67) |
| Other professional qualifications | 8198 (12.84) | 20749 (23.09) | 15 (0.03) |
| NVQ, HND, HNC or equivalent | 1456 (2.28) | 21176 (23.57) | 3071 (5.39) |
| College/university degree | 54172 (84.87) | 1035 (1.15) | 88 (0.15) |
| **Occupational attainment** |  |  |  |
| Unemployed or SEC 7 | 4001 (6.27) | 9798 (10.90) | 24707 (43.39) |
| SEC 4–6 | 4202 (6.58) | 18036 (20.07) | 19243 (33.79) |
| SEC 3 | 3737 (5.85) | 22337 (24.86) | 8432 (14.81) |
| SEC 2 | 24539 (38.45) | 26719 (29.74) | 3405 (5.98) |
| SEC 1.2 or SEC 1.1 | 27347 (42.85) | 12967 (14.43) | 1161 (2.04) |
| **Time spent watching TV (hours/day)** |  |  |  |
| ≥4 | 10042 (15.73) | 33679 (37.48) | 35437 (62.23) |
| 3–3.9 | 13945 (21.85) | 26325 (29.30) | 11612 (20.39) |
| 2–2.9 | 20252 (31.73) | 20694 (23.03) | 6800 (11.94) |
| <2 | 19587 (30.69) | 9159 (10.19) | 3099 (5.54) |
| **Frequency of confiding** |  |  |  |
| Never or almost never | 7646 (11.98) | 13718 (15.27) | 12639 (22.19) |
| About once a month or less | 7448 (11.67) | 10483 (11.67) | 6077 (10.67) |
| 1–4 times a week | 13749 (21.54) | 18313 (20.38) | 9614 (16.88) |
| Almost daily | 34983 (54.81) | 47343 (52.69) | 28618 (50.25) |
| **Frequency of social connection** |  |  |  |
| About once a month or less | 14112 (22.11) | 13893 (15.46) | 9669 (16.98) |
| About once a week | 22025 (34.51) | 28934 (32.20) | 17523 (30.77) |
| 2–4 times a week | 20771 (32.54) | 33871 (37.69) | 19304 (33.90) |
| Almost daily | 6918 (10.84) | 13159 (14.64) | 10452 (18.35) |
| **Variety of leisure activity engagement (/week)** | |  |  |
| 0 | 13458 (21.09) | 22909 (25.49) | 22568 (39.63) |
| 1 | 25418 (39.82) | 39990 (44.50) | 27082 (47.56) |
| 2–5 | 24950 (39.09) | 26958 (30.00) | 7298 (12.82) |

Abbreviations: CSE, Certificate of Secondary Education; GCSE, General Certificate of Secondary Education; NVQ, National Vocational Qualification; HND, Higher National Diploma; HNC, Higher National Certificate; SEC, socio-economic classification

**Supplementary Table 3** The 10th percentile differences (PDs) and 95% confidence intervals in time (years) to dementia onset in relation to cognitive reserve: results from Laplace regression (n=210,631)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Cognitive reserve** | **All-cause dementia** | |  | **Alzheimer’s disease** | |  | **Vascular dementia** | |
| Basic-adjusted  10th PD (95% CI)a | Multi-adjusted  10th PD (95% CI)b | Basic-adjusted  10th PD (95% CI)a | Multi-adjusted  10th PD (95% CI)b | Basic-adjusted  10th PD (95% CI)a | Multi-adjusted  10th PD (95% CI)b |
| Low | 0.00 (Reference) | 0.00 (Reference) |  | 0.00 (Reference) | 0.00 (Reference) |  | 0.00 (Reference) | 0.00 (Reference) |
| Moderate | 1.18 (0.96, 1.40) | 0.88 (0.65, 1.10) |  | 0.99 (0.69, 1.28) | 0.82 (0.51, 1.13) |  | 1.49 (1.09, 1.89) | 0.97 (0.57, 1.37) |
| High | 2.04 (1.79, 2.29) | 1.62 (1.35, 1.88) |  | 2.02 (1.66, 2.37) | 1.76 (1.38, 2.13) |  | 3.14 (2.63, 3.65) | 2.16 (1.64. 2.69) |

aModels were adjusted for age, gender, and ethnicity.

bModels were further adjusted for smoking status, alcohol consumption, physical activity, body mass index, hypertension, diabetes, heart disease, stroke, and genetic risk.

**Supplementary Table 4** Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia in relation to cognitive reserve and genetic risk in basic-adjusted Cox models (n=210,631)

|  |  |  |  |
| --- | --- | --- | --- |
| **Exposures** | Basic-adjusted HR (95% CI) | | |
| All-cause dementia | Alzheimer’s disease | Vascular dementia |
| **Cognitive reserve** |  |  |  |
| Low | Reference | Reference | Reference |
| Moderate | 0.73 (0.69, 0.77) | 0.75 (0.69, 0.82) | 0.65 (0.58, 0.73) |
| High | 0.58 (0.54, 0.62) | 0.57 (0.51, 0.63) | 0.42 (0.36, 0.48) |
| **Genetic risk** |  |  |  |
| Low | Reference | Reference | Reference |
| Moderate | 1.37 (1.27, 1.48) | 1.52 (1.33, 1.73) | 1.37 (1.18, 1.60) |
| High | 3.31 (3.10, 3.54) | 5.03 (4.49, 5.62) | 2.98 (2.60, 3.41) |

Models were adjusted for age, gender, and ethnicity.

**Supplementary Table 5** Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia in relation to cognitive reserve (CR), stratified according to genetic risk category (n=210,631)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **CR** | **All-cause dementia** (n = 6371) | |  | **Alzheimer’s disease** (n = 2767) | |  | **Vascular dementia** (n = 1490) | |
| HR (95% CI)a | HR (95% CI)b | HR (95% CI)a | HR (95% CI)b | HR (95% CI)a | HR (95% CI)b |
| **Low genetic risk** | |  |  |  |  |  |  |  |
| Low CR | Reference | Reference |  | Reference | Reference |  | Reference | Reference |
| Moderate CR | 0.75 (0.65, 0.85) | 0.84 (0.74, 0.96) |  | 0.74 (0.59, 0.93) | 0.83 (0.66, 1.05) |  | 0.67 (0.52, 0.87) | 0.80 (0.61, 1.03) |
| High CR | 0.56 (0.48, 0.66) | 0.68 (0.57, 0.79) |  | 0.52 (0.39, 0.68) | 0.61 (0.45, 0.81) |  | 0.36 (0.26, 0.51) | 0.49 (0.34, 0.70) |
| **Moderate genetic risk** | |  |  |  |  |  |  |  |
| Low CR | Reference | Reference |  | Reference | Reference |  | Reference | Reference |
| Moderate CR | 0.69 (0.62, 0.77) | 0.76 (0.67, 0.85) |  | 0.71 (0.59, 0.86) | 0.77 (0.63, 0.93) |  | 0.64 (0.51, 0.81) | 0.76 (0.60, 0.95) |
| High CR | 0.57 (0.50, 0.65) | 0.67 (0.59, 0.77) |  | 0.54 (0.43, 0.67) | 0.61 (0.48, 0.77) |  | 0.46 (0.35, 0.61) | 0.62 (0.47, 0.82) |
| **High genetic risk** | |  |  |  |  |  |  |  |
| Low CR | Reference | Reference |  | Reference | Reference |  | Reference | Reference |
| Moderate CR | 0.74 (0.69, 0.80) | 0.79 (0.74, 0.85) |  | 0.77 (0.69, 0.85) | 0.79 (0.71, 0.88) |  | 0.64 (0.55, 0.75) | 0.74 (0.63, 0.86) |
| High | 0.59 (0.54, 0.64) | 0.65 (0.59, 0.71) |  | 0.59 (0.52, 0.67) | 0.61 (0.54, 0.69) |  | 0.41 (0.34, 0.49) | 0.51 (0.42, 0.63) |

aModels were adjusted for age, gender, and ethnicity.

bModels were further adjusted for smoking status, alcohol consumption, physical activity, body mass index, hypertension, diabetes, heart disease, and stroke.

**Supplementary Table 6** The 10th percentile differences (PDs) and 95% confidence intervals in time (years) to dementia onset in relation to cognitive reserve (CR), stratified according to genetic risk category (n=210,631)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **CR** | **All-cause dementia** (n = 6371) | |  | **Alzheimer’s disease** (n = 2767) | |  | **Vascular dementia** (n = 1490) | |
| 10th PD (95% CI)a | 10th PD (95% CI)b | 10th PD (95% CI)a | 10th PD (95% CI)b | 10th PD (95% CI)a | 10th PD (95% CI)b |
| **Low genetic risk** | |  |  |  |  |  |  |  |
| Low CR | 0.00 (Reference) | 0.00 (Reference) |  | 0.00 (Reference) | 0.00 (Reference) |  | 0.00 (Reference) | 0.00 (Reference) |
| Moderate CR | 1.04 (0.56, 1.53) | 0.58 (0.09, 1.08) |  | 1.03 (0.24, 1.81) | 0.60 (-0.21, 1.41) |  | 1.31 (0.43, 2.18) | 0.71 (-0.17, 1.59) |
| High CR | 2.10 (1.51, 2.67) | 1.38 (0.78, 1.98) |  | 2.30 (1.34, 3.26) | 1.69 (0.69, 2.69) |  | 3.40 (2.24, 4.57) | 2.31 (1.15, 3.48) |
| **Moderate genetic risk** | |  |  |  |  |  |  |  |
| Low CR | 0.00 (Reference) | 0.00 (Reference) |  | 0.00 (Reference) | 0.00 (Reference) |  | 0.00 (Reference) | 0.00 (Reference) |
| Moderate CR | 1.31 (0.90, 1.72) | 0.99 (0.57, 1.41) |  | 1.05 (0.44, 1.66) | 0.84 (0.21, 1.47) |  | 1.41 (0.66, 2.16) | 0.89 (0.11, 1.67) |
| High CR | 1.99 (1.51, 2.46) | 1.43 (0.95, 1.91) |  | 2.04 (1.31, 2.78) | 1.60 (0.84, 2.36) |  | 2.60 (1.68, 3.53) | 1.58 (0.60, 2.55) |
| **High genetic risk** | |  |  |  |  |  |  |  |
| Low CR | 0.00 (Reference) | 0.00 (Reference) |  | 0.00 (Reference) | 0.00 (Reference) |  | 0.00 (Reference) | 0.00 (Reference) |
| Moderate CR | 1.19 (0.88, 1.50) | 0.92 (0.61, 1.12) |  | 0.95 (0.57, 1.33) | 0.84 (0.45, 1.23) |  | 1.58 (1.02, 2.14) | 1.13 (0.55, 1.71) |
| High | 2.14 (1.74, 2.52) | 1.73 (1.38, 2.09) |  | 1.92 (1.47, 2.38) | 1.80 (1.32, 2.26) |  | 3.30 (2.58, 4.01) | 2.40 (1.66, 3.15) |

aModels were adjusted for age, gender, and ethnicity.

bModels were further adjusted for smoking status, alcohol consumption, physical activity, body mass index, hypertension, diabetes, heart disease, and stroke.

**Supplementary Table 7** Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia in relation to joint exposure of genetic risk and cognitive reserve (n=210,631)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Joint exposure** | | **No. of subjects** | **Dementia** | | |
| Genetic risk | Cognitive reserve | Cases | HR (95% CI)a | HR (95% CI)b |
| Low | High | 21250 | 253 | Reference | Reference |
| Low | Moderate | 30142 | 471 | 1.31 (1.13, 1.53) | 1.26 (1.08, 1.47) |
| Low | Low | 18751 | 419 | 1.75 (1.50, 2.05) | 1.55 (1.33, 1.81) |
| Moderate | High | 21500 | 365 | 1.44 (1.23, 1.69) | 1.44 (1.23, 1.70) |
| Moderate | Moderate | 29825 | 602 | 1.70 (1.47, 1.97) | 1.64 (1.42, 1.90) |
| Moderate | Low | 19025 | 596 | 2.46 (2.12, 2.85) | 2.18 (1.88, 2.53) |
| High | High | 21076 | 819 | 3.36 (2.92, 3.87) | 3.39 (2.94, 3.90) |
| High | Moderate | 29890 | 1480 | 4.30 (3.76, 4.91) | 4.14 (3.62, 4.73) |
| High | Low | 19172 | 1366 | 5.80 (5.07, 6.64) | 5.16 (4.50, 5.90) |

aModels were adjusted for age, gender, and ethnicity.

bModels were further adjusted for smoking status, alcohol consumption, physical activity, body mass index, hypertension, diabetes, heart disease, and stroke.

**Supplementary Table 8** Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia in relation to joint exposure of apolipoprotein E ε4 allele and cognitive reserve

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Joint exposure** | | | **No. of subjects** | **Dementia** | | |
| Apolipoprotein E ε4 allele | | Cognitive reserve | Cases | HR (95% CI)a | HR (95% CI)b |
| Non-carriers | High | | 56611 | 937 | Reference | Reference |
| Non-carriers | Moderate | | 59041 | 1068 | 1.87 (0.99, 1.19) | 1.06 (0.97, 1.16) |
| Non-carriers | Low | | 41539 | 1210 | 1.65 (1.51, 1.80) | 1.50 (1.38, 1.64) |
| Carriers | High | | 15374 | 656 | 2.64 (2.39, 2.92) | 2.70 (2.45, 2.99) |
| Carriers | Moderate | | 24613 | 1407 | 3.55 (3.27, 3.86) | 3.42 (3.15, 3.72) |
| Carriers | Low | | 13453 | 1092 | 4.73 (4.33, 5.16) | 4.26 (3.90, 4.65) |

aModels were adjusted for age, gender, and ethnicity.

bModels were further adjusted for smoking status, alcohol consumption, physical activity, body mass index, hypertension, diabetes, heart disease, and stroke.

**Supplementary Table 9** Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia in relation to each cognitive reserve-related factor (n=210,631)

|  |  |  |
| --- | --- | --- |
| **Cognitive reserve-related factors** | **Dementia** | |
| HR (95% CI)a | HR (95% CI)b |
| **Education** |  |  |
| No educational qualifications | Reference | Reference |
| CSEs, O levels/GCSE, A levels/AS levels or equivalent | 0.76 (0.71, 0.82) | 0.81 (0.76, 0.87) |
| Other professional qualifications | 0.70 (0.71, 0.82) | 0.76 (0.70, 0.82) |
| NVQ, HND, HNC or equivalent | 0.75 (0.69, 0.82) | 0.81 (0.75, 0.89) |
| College/university degree | 0.62 (0.58, 0.66) | 0.69 (0.65, 0.74) |
| **Occupational attainment** |  |  |
| Unemployed or SEC 7 | Reference | Reference |
| SEC 4–6 | 0.74 (0.67, 0.77) | 0.78 (0.72, 0.83) |
| SEC 3 | 0.63 (0.58, 0.68) | 0.69 (0.64, 0.75) |
| SEC 2 | 0.60 (0.56, 0.64) | 0.68 (0.64, 0.73) |
| SEC 1.2 or SEC 1.1 | 0.51 (0.47, 0.55) | 0.60 (0.56, 0.66) |
| **Time spent watching television (hours/day)** |  |  |
| ≥4 | Reference | Reference |
| 3–3.9 | 0.79 (0.74, 0.84) | 0.84 (0.79, 0.90) |
| 2–2.9 | 0.75 (0.70, 0.80) | 0.81 (0.75, 0.86) |
| <2 | 0.69 (0.64, 0.75) | 0.75 (0.69, 0.81) |
| **Frequency of confiding** |  |  |
| Never or almost never | Reference | Reference |
| About once a month or less | 0.96 (0.88, 1.05) | 0.98 (0.91, 1.07) |
| 1–4 times a week | 0.87 (0.81, 0.94) | 0.91 (0.84, 0.98) |
| Almost daily | 0.75 (0.70, 0.80) | 0.79 (0.74, 0.84) |
| **Frequency of social connection** |  |  |
| About once a month or less | Reference | Reference |
| About once a week | 0.92 (0.85, 0.98) | 0.94 (0.88, 1.01) |
| 2–4 times a week | 0.79 (0.74, 0.85) | 0.81 (0.76, 0.88) |
| Almost daily | 0.92 (0.85, 1.004) | 0.91 (0.84, 0.99) |
| **Variety of leisure activity engagement (/week)** |  |  |
| ≤0 | Reference | Reference |
| 1 | 0.86 (0.81, 0.91) | 0.91 (0.86, 0.97) |
| 2–5 | 0.67 (0.63, 0.72) | 0.75 (0.70, 0.80) |

aModels were adjusted for age, gender, and ethnicity.

bModels were further adjusted for smoking status, alcohol consumption, physical activity, body mass index, hypertension, diabetes, heart disease, stroke, and genetic risk.

Abbreviations: CSE, Certificate of Secondary Education; GCSE, General Certificate of Secondary Education; NVQ, National Vocational Qualification; HND, Higher National Diploma; HNC, Higher National Certificate; SEC, socio-economic classification

**Supplementary Table 10** Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia in relation to cognitive reserve using competing risk models (n=210,631)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cognitive reserve** | No. of subjects | **Dementia** | | |
| No. of cases | HR (95% CI)a | HR (95% CI)b |
| Low | 56948 | 2381 | Reference | Reference |
| Moderate | 89857 | 2553 | 0.75 (0.71, 0.80) | 0.81 (0.76, 0.86) |
| High | 63826 | 1437 | 0.61 (0.57, 0.65) | 0.68 (0.63, 0.73) |

aModels were adjusted for age, gender, and ethnicity.

bModels were further adjusted for smoking status, alcohol consumption, physical activity, body mass index, hypertension, diabetes, heart disease, stroke, and genetic risk.

**Supplementary Table 11** Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia at least 5 years after baseline in relation to cognitive reserve (n=210,037)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cognitive reserve** | No. of subjects | **Dementia** | | |
| No. of cases | HR (95% CI)a | HR (95% CI)b |
| Low | 56731 | 2164 | Reference | Reference |
| Moderate | 89622 | 2318 | 0.72 (0.68, 0.77) | 0.79 (0.74, 0.84) |
| High | 63684 | 1295 | 0.57 (0.53, 0.61) | 0.65 (0.60, 0.70) |

aModels were adjusted for age, gender, and ethnicity.

bModels were further adjusted for smoking status, alcohol consumption, physical activity, body mass index, hypertension, diabetes, heart disease, stroke, and genetic risk.



**Supplementary Figure 1** Flowchart of the study population

Abbreviations: CR, cognitive reserve