




Genetic Risk of Dementia Mitigated by Cognitive Reserve: A Cohort Study

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Objective: We investigated whether cognitive reserve modifies the risk of dementia attributable to apolipoprotein $\epsilon 4$ (*APOE- $\epsilon 4$*), a well-known genetic risk factor for dementia.

Methods: We followed 2,556 cognitively intact participants aged ≥ 60 years from the ongoing prospective community-based Swedish National Study on Aging and Care in Kungsholmen (SNAC-K). Dementia was ascertained through clinical and neuropsychological assessments and diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria. Structural equation modeling was used to generate a cognitive reserve indicator from 4 previously validated contributors: early life education, midlife substantive work complexity, late life leisure activities, and late life social networks. Cox proportional hazard models estimated dementia risk in relation to cognitive reserve indicator. The interaction between the cognitive reserve indicator and *APOE- $\epsilon 4$* was assessed on multiplicative and additive scales.

Results: After an average of 6.3 years (range = 2.1–10.7) of follow-up, 232 dementia cases were ascertained. Relative to individuals in the lowest tertile of cognitive reserve indicator, those with moderate and high reserve were at a reduced risk of dementia. There was no multiplicative interaction between *APOE- $\epsilon 4$* status and cognitive reserve indicator ($p = 0.113$). Additive interaction was statistically significant. Relative to *APOE- $\epsilon 4$* carriers with low cognitive reserve, $\epsilon 4$ carriers with high reserve had a reduced risk of dementia (hazard ratio [HR] = 0.28, 95% confidence interval [CI] = 0.13–0.59). The magnitude of risk reduction was similar in $\epsilon 4$ noncarriers with a high cognitive reserve indicator (HR = 0.24, 95% CI = 0.15–0.40).

Interpretation: Lifelong engagement in reserve-enhancing activities attenuates the risk of dementia attributable to *APOE- $\epsilon 4$* . Promoting cognitive reserve might be especially effective in subpopulations with high genetic risk of dementia.

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Cognitive reserve has been proposed to account for the mismatch between the extent of brain damage and its clinical manifestation in the form of dementia diagnosis.¹ People with more reserve might withstand dementia pathology as a result of active compensatory mechanisms that enhance brain network efficiency and flexibility.² Education, but also stimulating occupational and social environments have been suggested as factors contributing to reserve.^{3,4}

Measuring cognitive reserve is often a challenging task.⁵ For instance, it is becoming increasingly clear that cognitive reserve develops from continued engagement in multiple activities throughout the life course.⁶ As a result, focusing on contributors occurring at a single period makes it difficult to

capture either the full effect of prolonged exposure, or the important modifying effects of several reserve-enhancing factors.^{7,8} In a previous study, we attempted to uncover the relative importance of life stages (early, mid-, and late life) at which exposure to reserve-enhancing factors was most associated with the risk of dementia.⁹ Due to the strong correlation between the early and the midlife reserve indicators, we were unable to assess the relative importance of each life period. However, we found that having a high reserve score in all 3 life stages was associated with the largest reduction in dementia risk.⁹ This suggested that continued engagement in activities with reserve-enhancing properties might be especially important.

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The interaction between lifelong cognitive reserve and genetic predisposition to dementia remains poorly understood. Some have suggested that carriers of the apolipoprotein $\epsilon 4$ (*APOE- $\epsilon 4$*) allele might be more susceptible to the beneficial effects of physical activities or healthy lifestyles,¹⁰ although this conclusion has not been universally supported.¹¹ Others, focusing on single contributors to reserve, such as education, have reported both increased protection in those with genetic risk¹² and equivalent levels of dementia risk reduction in both $\epsilon 4$ carriers and noncarriers with high education.¹³ A comprehensive examination of cognitive reserve's ability to mitigate $\epsilon 4$ -related risk in a large population-based cohort comprising reserve contributors from several stages over the life course, as well as a clinically ascertained diagnosis of dementia, is yet to be attempted.

Building on our previous work, the aim of this study is to generate a lifelong cognitive reserve indicator that is not specific to life stage, but that emphasizes the accumulation of mental and social inputs across the entire life course. Importantly, and in contrast with our previous study, in deriving this measure we also extract information on late life social network, which has been repeatedly suggested as a viable input into cognitive reserve.^{14,15} Our reserve indicator incorporates education (early adulthood), substantive work complexity (accumulated across 5 occupations in midlife), social network (late life), and leisure activities (late life). Using a different study population that is not just larger, but also much more diverse with respect to gender and age/birth cohort mix, we examine the association between the cumulative measure of cognitive reserve and dementia risk over an average of 6 years of follow-up. Finally, as an expansion of our previous work, we explore in much greater detail the relationship between cumulative cognitive reserve and genetic predisposition to dementia (*APOE- $\epsilon 4$* status).

Subjects and Methods

Study Population

The study population was from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), an ongoing community-based longitudinal study of adults aged ≥ 60 years, living at home or in an institution in a district of Stockholm between 2001 and 2004.¹⁶ This study population is different from the Kungsholmen Project¹⁷ data used in our previous study, which was both smaller and less heterogeneous with respect to age/gender mix. SNAC-K participants were randomly drawn from 11 age cohorts. At baseline, 3,363 individuals (participation rate = 73.3%) underwent nurse interviews, clinical examinations, cognitive assessments, and laboratory testing. Participants aged 60 to 72 years were re-examined every 6 years, whereas those aged ≥ 78 years were re-examined every 3 years. For cognitively impaired

subjects, a proxy or a caregiver was interviewed. SNAC-K was approved by the Regional Ethical Review Board in Stockholm, and written informed consent was obtained from participants or their next of kin.

Of the 3,363 participants, 322 were diagnosed with dementia at baseline and were excluded from the study. Individuals who did not attend any of the follow-up examinations ($n = 272$) and those with schizophrenia or developmental disorders ($n = 16$) were excluded, resulting in 2,753 subjects eligible for inclusion (see Fig 1 for flowchart). After removing 197 participants with missing data on covariates, the study population amounted to 2,556 individuals. The average follow-up time was 6.3 years (range = 2.1–10.7).

Dementia Diagnosis

Dementia was ascertained through clinical and cognitive examinations administered according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria. A 3-step procedure was employed,¹⁸ where 2 physicians working independently made a preliminary diagnosis and a third opinion was sought from the senior neurologist in the event of discordant assessments. For deceased participants, dementia diagnosis was based on death certificates, hospital discharge registers, and hospital records.

Assessment of Cognitive Reserve Indicator over the Life Course

An indicator of cognitive reserve combined 4 measures of stimulating mental, social, and physical environments over the life course: early life education, midlife substantive work complexity, and indices of late life social network and leisure activities.

Years of Education (Early Life). Years of education were assessed during the nurse interview at baseline. The levels of education and their corresponding mean durations were unfinished primary (7 years), elementary (9.5 years), vocational training (11 years), high school (11.6 years), unfinished higher education (13.8 years), completed university (16.1 years), and doctoral studies (20.6 years).

Substantive Work Complexity (Midlife). During the baseline interview, participants were inquired about their 5 longest-held occupations, which we ranked according to substantive complexity. Substantively complex occupations require thought and independent judgment, especially when making decisions involving poorly defined outcomes.¹⁹ Substantive complexity ratings were originally derived from the US Dictionary of Occupational Titles and were matched with analogous Swedish occupations by 2 independent raters, one based in the United States and the other in Sweden.²⁰ Mean complexity score across all reported occupations throughout life indicated accumulated complexity. The resulting variable was a continuous score ranging from 0.7 to 10 (higher values indicated greater substantive complexity).

Social Network Index (Late Life). Aspects of social network were considered along the dimensions of size and support in accordance with a previously validated procedure.²¹ To capture network size, we used information on marital status, living arrangement, number of

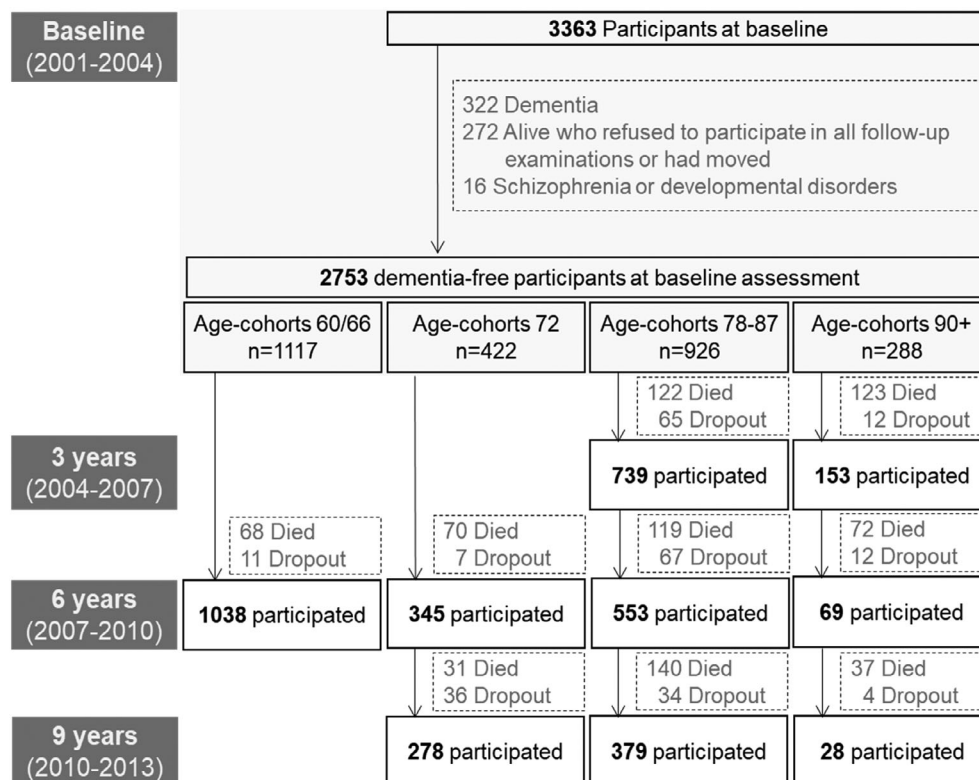


FIGURE 1: Flowchart of study population in SNAC-K (Swedish National Study on Aging and Care in Kungsholmen). Baseline dementia cases ($n = 322$) include both definite ($n = 252$) and questionable cases ($n = 70$). Dementia status was available for deceased study participants as a result of comprehensive assessment of inpatient and cause of death records. Age-cohort 60/66 is composed of individuals aged 60 and 66 years at baseline who were followed up after six years. Age-cohort 72 is made up of individuals aged 72 years at baseline who were followed up for the first time after six years and then three years after that. Age-cohort 78-87 includes individuals aged 78, 81, 84, 87 years who were followed-up every three years since baseline. Age cohort 90+ is made up of individuals aged 90 years or older at baseline who were followed up every three years.

children, frequency of contact with relatives or friends, and the number of contacts available to turn to. Network support was assessed by inquiring about satisfaction with social connections, the extent of perceived material and psychosocial support received, and the sense of affinity and belonging to the various groups. All indicators were converted into z scores and averaged separately across the components of network size and support. Because the correlation between the two measures was considerable (0.76), we computed the social network index by averaging the 2 subindices. The resulting variable was a continuous score ranging from -2 to 1.22 (high scores indicate richer social network).

Leisure Activities Index (Late Life). During the baseline interview, participants were read a list of 26 activities and were instructed to indicate which ones they practiced and specify the frequency of engagement over the preceding year. Leisure activities were categorized as mental, social, or physical. For the mental and social components, the richness of engagement was categorized into 3 levels (low, moderate, high) according to the number of activities performed (mental component: low engagement [≤ 1 activity], moderate engagement [2–3 activities], and high [≥ 4 activities]; social component: low engagement [no activities], moderate engagement [1 activity], high engagement [≥ 2 activities]). For the physical component, richness was defined based on the frequency of engagement and

categorized as: low (less than once per week), moderate (at least once per week), and high (more than once per week). As a previous study has reported similar dementia risk reduction across all 3 leisure components, with the largest protection being associated with rich engagement in all domains,¹⁵ we generated a global measure of leisure richness by summing the mental, social, and physical scores, resulting in a continuous variable (range = 0–6; higher scores denote greater leisure engagement).

Genetic Predisposition

Genomic DNA was extracted from peripheral blood samples collected at baseline. *APOE* allelic status was determined using a microsequencing method (AffiGen *APOE*; Sangtec Medical, Stockholm, Sweden) based on a polymerase chain reaction with biotinylated primers.²² *APOE-ε4* status was dichotomized (any $\epsilon 4$ carriers vs noncarriers) in the analysis.

Covariates

In addition to age and sex, we considered smoking, body mass index (BMI), hypertension, cerebro- and cardiovascular diseases, and diabetes. Disease status came from physician examinations, medication use, and the Swedish National Patient Register. Vital status came from the Swedish Cause of Death Register and hospital discharge records.

Statistical Analysis

Structural equation modeling (SEM) was performed to derive a best-fitting measurement model incorporating the 4 observed factors occurring over the life course: education, substantive complexity, social network, and leisure activities. Model fit was assessed using χ^2 goodness of fit, the comparative fit index, and the root mean square error of approximation. Omitted paths were explored using modification indices. Predicted values of the latent variable, called the *reserve indicator*, were obtained by summing the products of standardized indicators and the corresponding SEM-factor score weights.

Minimally (age, sex) and fully adjusted (smoking, BMI, heart disease, hypertension, cerebrovascular diseases, diabetes, and *APOE-ε4* status) Cox proportional hazard models estimated the risk of dementia conditional on the cognitive reserve indicator predicted from the SEM. The reserve indicator was operationalized continuously and categorically (tertile distribution; reference: bottom tertile). Follow-up time was computed as time since entry until dementia diagnosis, death, or the last examination.

Both multiplicative and additive interactions between reserve indicator and *APOE-ε4* status were examined. Because estimation of the additive interaction may be biased when preventive factors are considered,²³ the reserve indicator was recoded as a binary risk factor (0: middle or top tertile; 1: bottom tertile) and excess risk of dementia in various strata of reserve and *ε4*-status was estimated relative to the most optimal scenario: “high reserve and *APOE*-non-*ε4*.” For the additive interaction, relative excess risk due to interaction, the attributable proportion, and the synergy index were computed. If statistically significant, these measures would suggest that the relative risk of dementia when the 2 factors were present was significantly greater than the sum of the relative risks associated with the presence of just the *ε4* allele or just the low score on the reserve indicator. This is in contrast with the multiplicative interaction, which would quantify the extent to which the effect of both exposures together exceeds the product of the effects of the 2 exposures considered separately. To further explore the interrelationship between reserve indicator and genetic predisposition, we generated a categorical variable designating 6 combinations of the life course reserve indicator (in tertiles: bottom, middle, top) and *APOE-ε4* status (no vs yes). We examined the effect of each level of this variable on dementia, relative to the group: “low reserve and *APOE-ε4*”.

In sensitivity analyses, multiple imputation by chained equation was used to impute data for 197 participants with missing data on covariates. Cox models were re-estimated without 86 incident dementia cases from the first follow-up to reduce potential bias of preclinical dementia at baseline. We also excluded 308 individuals with possible cognitive impairment (Mini-Mental State Examination [MMSE] \leq 27).

Results

After an average of 6.3 years (range = 2.1–10.7) of follow-up of 2,556 participants (15,606 person-years), 232 dementia

cases were ascertained (incidence rate = 14.9 cases per 1,000 person-years; 95% confidence interval [CI] = 13.1–16.9). Baseline characteristics of the study population according to incident dementia status are in Table 1. Additionally, tabulating baseline characteristics according to *APOE-ε4* status (not presented) revealed that *ε4* carriers were slightly younger at baseline (72.1 vs. 73.8 years) and more likely to smoke (proportion current/ever smoking: 56.9% [*APOE-ε4* carrier] vs 52.1% [noncarrier]). Baseline MMSE levels did not differ across *APOE-ε4* subsamples, suggesting limited selection of cognitively impaired participants with *ε4* allele into the study.

The 197 individuals who were excluded due to missing data on covariates did not differ from the analyzed population with respect to sex (odds ratio [OR] = 1.00, 95% CI = 0.72–1.39) or the probability of university education (OR = 0.64, 95% CI = 0.40–1.01). They were more likely to be older (OR = 1.05, 95% CI = 1.03–1.06) and had more cerebrovascular disorders (OR = 1.81, 95% CI = 1.16–2.84).

The best-fitting SEM with 4 cognitive reserve-enhancing factors is presented in Figure 2. A unique value of the latent variable was predicted for each individual using the SEM factor score weights, and the resulting continuous variable, the *reserve indicator*, was normally distributed with a mean of zero (range = –4.28 to 3.62).

In the basic adjusted model (age cohort and sex), the continuous operationalization of the cognitive reserve indicator, predicted from SEM, was associated with a reduced risk of dementia over the follow-up (Table 2, first row). This association was only marginally attenuated in the multadjusted model.

In a categorical specification, relative to those in the bottom tertile of the reserve indicator, the middle and the top tertiles were at a reduced risk of dementia (see Table 2, rows 2–4). The dose-response trend was statistically significant ($p < 0.01$). Adjustment for health behaviors, comorbidities, and genetic predisposition did not alter the results.

The multiplicative interaction between the continuous reserve indicator and *APOE-ε4* did not reach statistical significance ($p = 0.113$). For the additive interaction, we recoded cognitive reserve indicator as a binary risk factor “low reserve” (0: middle or top tertile vs 1: bottom tertile of reserve) to avoid biased computation in the presence of preventive factors with relative risks below 1. The relative excess risk due to interaction (1.28, 95% CI = 0.19–2.36), the attributable proportion due to interaction (0.38, 95% CI = 0.12–0.64), and the synergy index (2.18, 95% CI = 1.01–4.72) all indicated the presence of an additive interaction (Table 3). This suggests that the relative risk of dementia when both low reserve and *APOE-ε4* were present was significantly greater than

TABLE 1. Baseline Characteristics of Study Population by Incident Dementia during Follow-up

Characteristic	Dementia-Free, n = 2324	Incident Dementia, n = 232	<i>p</i>
Demographics			
Age, yr	72.3 ± 10.1	82.7 ± 6.8	<0.001
60–66	1,066 (45.9)	3 (1.3)	
72–78	704 (30.3)	85 (36.7)	
81–87	378 (16.2)	87 (37.5)	
90+	176 (7.6)	57 (24.5)	
Female	1,435 (61.8)	162 (69.8)	0.015
Education			
Elementary	328 (14.1)	46 (19.8)	<0.001
Professional schools	968 (41.7)	126 (54.3)	
High school	233 (10.0)	19 (8.2)	
University	794 (34.2)	41 (17.7)	
VRFs and medical conditions			
Current/ever smoking	1,255 (54.0)	111 (47.8)	0.073
Alcohol consumption	1,633 (70.5)	109 (47.2)	<0.001
BMI, kg/m ²			
Underweight, <20	112 (4.8)	28 (12.1)	<0.001
Normal, 20–24.9	917 (41.8)	115 (49.6)	
Overweight, 25–29.9	941 (40.4)	72 (31.0)	
Obese, ≥30	300 (12.9)	17 (7.3)	
Hypertension	1,627 (70.0)	166 (71.5)	0.624
Heart diseases	516 (22.2)	103 (37.1)	0.001
Cerebrovascular diseases	127 (5.5)	38 (13.8)	0.001
Type 2 diabetes	190 (8.2)	37 (14.7)	0.007
Any <i>APOE</i> ε4	640 (27.5)	89 (37.9)	0.001
MMSE	28.9 ± 1.34	27.4 ± 2.01	<0.001
Cognitive reserve-enhancing factors			
Years of education	12.3 ± 4.0	10.7 ± 3.6	<0.001
Work complexity score	5.0 ± 1.8	4.4 ± 1.8	<0.001
Leisure activities score	2.51 ± 1.47	1.69 ± 1.34	<0.001
Social network score	0.09 ± 0.51	−0.19 ± 0.6	<0.001

Data are presented as mean ± standard deviation or number (%).
APOE ε4 = apolipoprotein ε4 allele; BMI = body mass index; MMSE = Mini-Mental State Examination; VRF = vascular risk factor.

the sum of the relative risks associated with the presence of just the ε4 allele or just the low score on the reserve indicator.

The joint effect of reserve indicator and *APOE*-ε4 status was further examined using categorical indicators (Fig 3). Relative to ε4 carriers with a low score on the

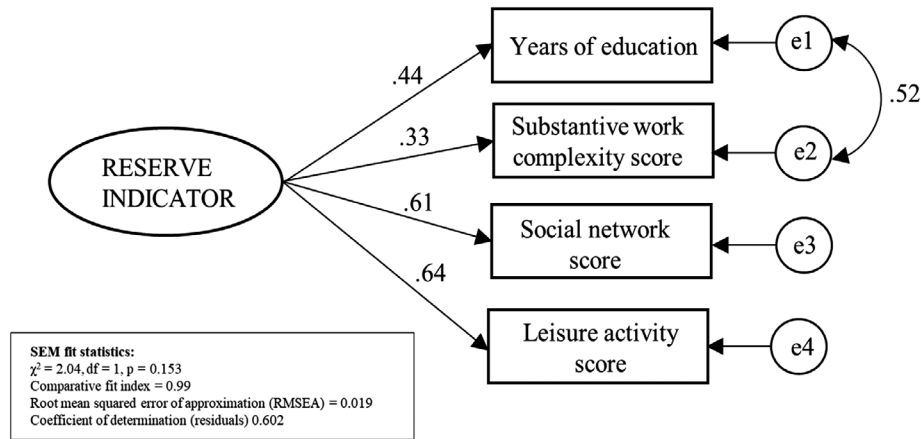


FIGURE 2: Standardized estimates from the structural equation model (SEM) with 4 observed cognitive reserve-enhancing factors. For years of education, range = 3 to 23 years. Substantive work complexity score is the average complexity score for all reported occupations during professional life (range = 0.7–10). Social network score was obtained by averaging z-standardized components of network size and network satisfaction. Leisure activity score was obtained by examining 26 leisure activities across mental/physical/social domains of leisure. For details about the operationalization of the cognitive reserve-enhancing factors, see the Subjects and Methods section.

TABLE 2. The Association between the Cognitive Reserve Indicator and Dementia

Reserve Indicator	Subjects, n	Cases, n	Basic Adjusted, HR (95% CI) ^a	p	Multiaadjusted, HR (95% CI) ^b	p
Continuous	2,556	232	0.76 (0.68–0.85)	<0.001	0.77 (0.69–0.86)	<0.001
By tertile						
Low	816	133	Reference		Reference	
Moderate	849	68	0.69 (0.51–0.93)	<0.001	0.68 (0.50–0.92)	0.011
High	891	41	0.40 (0.27–0.60)	<0.001	0.42 (0.28–0.63)	<0.001
p for trend			0.65 (0.54–0.78)	<0.001	0.65 (0.54–0.79)	<0.001

Cox proportional hazard models. Separate Cox models estimated for continuous and categorical versions of reserve indicator.
^aAdjusted for age cohorts and sex.
^bAdjusted for age cohorts, sex, smoking, body mass index, heart disease, hypertension, cerebrovascular diseases, diabetes, and *APOE-ε4*.
 CI = confidence interval; HR = hazard ratio.

cognitive reserve indicator (bottom tertile), $\epsilon 4$ carriers with moderate reserve had a reduced risk of dementia (hazard ratio [HR] = 0.60, 95% CI = 0.37–0.96). *APOE-ε4* carriers with a high reserve indicator score were at a further reduced risk (HR = 0.28, 95% CI = 0.13–0.59). *APOE-ε4* noncarriers had their dementia risk reduced proportionally to an increase in the cognitive reserve indicator, from low (HR = 0.48, 95% CI = 0.34–0.69), through moderate (HR = 0.35, 95% CI = 0.23–0.53), to high (HR = 0.24, 95% CI = 0.15–0.40).

The substantive conclusions remained unchanged after excluding 86 individuals with incident dementia at the first follow-up, or omitting 308 participants with baseline MMSE ≤ 27 (Tables 4 and 5).

Discussion

In this population-based prospective study, we found that a cognitive reserve indicator comprised of 4 observed factors over the life course—education, substantive work complexity, social network, and leisure activities—was associated with a reduced risk of dementia in a dose-response manner. Additive interaction between the reserve indicator and *APOE-ε4* status was observed. When combinations of the reserve indicator and genetic risk were examined, cognitive reserve appeared to override the detrimental effect of genetic predisposition, as the risk of dementia among *APOE-ε4* carriers was similar to that of the noncarriers.

Protective effects of single-factor measures of cognitive reserve on dementia, such as higher education or

TABLE 3. Combined Effect of Dichotomized Reserve Indicator (High vs Low) and Genetic Risk of Dementia (Any APOE-ε4 Carrier vs Noncarrier) Used for the Calculation of Additive Interaction

Joint Effect			Basic Adjusted ^a		Multiadjusted ^b	
Cognitive Reserve	APOE-ε4	Subjects (cases)	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
High	No	1,236 (65)	Reference		Reference	
Low	No	592 (79)	1.53 (1.09–2.14)	0.014	1.56 (1.11–2.19)	0.010
High	Yes	504 (34)	1.56 (1.03–2.37)	0.036	1.54 (1.01–2.34)	0.043
Low	Yes	224 (54)	3.30 (2.29–4.74)	<0.001	3.25 (2.25–4.69)	<0.001

Measures of additive interaction (from the model with multiple confounder adjustment): relative excess risk due to interaction, 1.276, 95% CI = 0.189–2.363; attributable proportion due to interaction, 0.380, 95% CI = 0.123–0.638; synergy index, 2.183, 95% CI = 1.010–4.720.

^aAdjusted for baseline age and sex.

^bAdjusted for baseline age cohorts, sex, smoking, body mass index, heart disease, hypertension, cerebrovascular diseases, and diabetes.

CI = confidence interval; HR = hazard ratio.

complex occupations, have been reported previously.³ Focusing on single reserve contributors makes it difficult to disentangle reserve pathways of efficiency or compensation from nonreserve mechanisms, for example those involving socioeconomic disadvantage. Instead, a shift toward more integrated measures, akin to a lifelong reserve indicator operationalized here using SEM, has been discussed in literature, although this approach is not without methodological and theoretical shortcomings.⁵ Cognitive reserve is modeled as a reflective indicator here, meaning that the measurement model treats observable factors whose shared covariation identifies the latent variable as downstream outcomes of the latent reserve construct. This causal ordering, however, is not entirely consistent with the theory of cognitive reserve according to which it is the

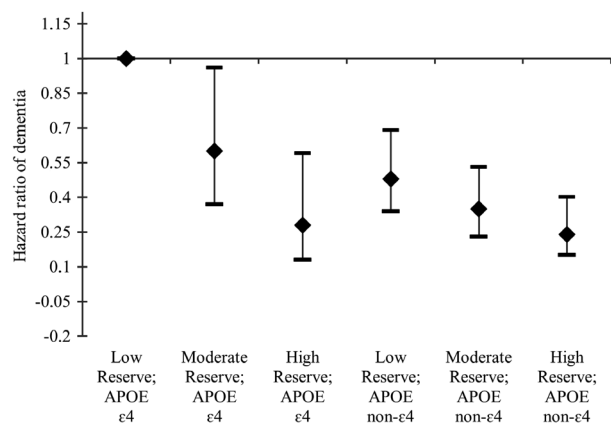


FIGURE 3: Combined effect of the cognitive reserve indicator and APOE-ε4 status on the risk of dementia estimated from a fully adjusted Cox proportional hazard model. Hazard ratios and 95% confidence intervals are shown. Multiple confounder adjustment included age cohort, sex, smoking, body mass index, heart disease, hypertension, cerebrovascular diseases, and diabetes.

unique contribution (and not the shared covariation) of lifelong inputs that forms the reserve. This suggests that cognitive reserve is a formative, rather than a reflective latent indicator.⁵ Respecifying reflective measurement models as formative is methodologically unfeasible, as the resulting specification becomes statistically indistinguishable from the multiple regression and does not allow for assessing the validity of the hypothesized latent variable. Even though several neuroimaging and clinicopathological studies have largely supported the presence of a neural basis for efficiency and compensation,^{24,25} there is still much need for methodological development of the cognitive reserve concept.²⁶

A life course perspective to cognitive reserve in dementia has been suggested previously,⁶ but only a handful of studies were able to implement it.²⁷ A recent study from our group has attempted to test the relevant importance of stages (early, mid-, and late life) at which cognitive reserve exerted the largest protection against dementia risk.⁹ Building on the findings from that study, which suggested that cumulative engagement in reserve-enhancing activities might be more relevant than the specific stages at which these contributors were acquired, we devised a cognitive reserve indicator that considered simultaneous contributions of several inputs. Among these, we also included social network and accumulated substantive complexity across 5 midlife occupations that were not considered in the previous study. Our findings confirmed that lifelong accumulation of stimulating experiences, supplying the reserve, is associated with the lowest risk of dementia and could be viewed as a viable prevention target.²⁷

Based on the SEM factor loads, it appeared that the contribution of late life inputs, specifically social network and leisure activities, to the cumulative cognitive reserve

TABLE 4. Sensitivity Analyses

Reserve Indicator	Subjects, n ^{a,b}	Cases, n ^{a,b}	Excluding Incident Dementia During First Follow-up		Excluding MMSE ≤ 27	
			HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Continuous	2,470 (2,248)	146 (143)	0.75 (0.65–0.86)	<0.001	0.75 (0.65–0.86)	<0.001
Low	761 (635)	78 (78)	Reference		Reference	
Moderate	824 (761)	43 (42)	0.69 (0.47–1.01)	0.058	0.63 (0.43–0.93)	0.021
High	885 (852)	25 (23)	0.45 (0.28–0.72)	0.001	0.42 (0.26–0.68)	<0.001
<i>p</i> for trend			0.67 (0.54–0.84)	<0.001	0.64 (0.51–0.82)	<0.001

Cox regression HRs and 95% CIs for the association between levels of cognitive reserve and dementia, multiple adjustment.

^aAfter excluding n = 86 participants with dementia at first follow-up.

^bAfter excluding n = 308 participants with MMSE ≤ 27.

Multiple confounder adjustment: age cohorts, sex, smoking, body mass index, heart disease, hypertension, cerebrovascular diseases, diabetes, and *APOE-ε4*.

TABLE 5. Sensitivity Analyses

Reserve Indicator	Joint Effect <i>APOE-ε4</i>	Subjects (cases), n ^a	Subjects (cases), n ^b	Excluding Incident Dementia during First Follow-up		Excluding MMSE ≤ 27	
				HR (95% CI) ^a	<i>p</i>	HR (95% CI) ^b	<i>p</i>
Low	Yes	206 (36)	174 (38)	Reference		Reference	
Moderate	Yes	247 (15)	236 (18)	0.49 (0.27–0.91)	0.025	0.53 (0.30–0.94)	0.031
High	Yes	245 (7)	235 (6)	0.29 (0.13–0.67)	0.004	0.24 (0.10–0.57)	0.001
Low	No	555 (42)	461 (40)	0.42 (0.27–0.66)	<0.001	0.36 (0.23–0.56)	<0.001
Moderate	No	577 (28)	525 (24)	0.36 (0.22–0.59)	<0.001	0.26 (0.15–0.44)	<0.001
High	No	640 (18)	617 (17)	0.24 (0.14–0.43)	<0.001	0.21 (0.11–0.37)	<0.001

HRs and 95% CIs of dementia for the combined effect of *APOE-ε4* in Cox models with different inclusion criteria. Multiple confounder adjustment: age cohorts, sex, smoking, body mass index, heart disease, hypertension, cerebrovascular diseases, and diabetes.

^aAfter excluding n = 86 participants with dementia at first follow-up.

^bAfter excluding n = 308 participants with MMSE ≤ 27.

CI = confidence interval; HR = hazard ratio; MMSE = Mini-Mental State Examination.

indicator was the largest. This is in agreement with our previous study where mental, social, and physical components of late life leisure also had high factor loadings. Notably, aspects of social network were not taken into account in that earlier analysis. It appears from these results that inputs into cognitive reserve continue well into old age and may be especially relevant at a time when protection afforded by the earlier sources of resilience (eg, education) will have been exhausted. However, some of this association may also reflect reverse causality between preclinical dementia and social network or leisure activities, whereby individuals in the early stages of the disease disengage from social participation.

However, sensitivity analysis in which we excluded incident dementia cases after 3 years of follow-up revealed only negligible deviation from the original results, strengthening the conclusions of this study.

Our study is one of the few to report evidence of an additive interaction between the composite cognitive reserve indicator and genetic predisposition to dementia (*APOE-ε4* status). It suggests that if the reserve indicator were to be expressed as a risk factor (ie, lowest tertile of the index, as selected here), the *APOE-ε4* subgroup of the population who also had low reserve would experience a risk of dementia that was significantly in excess of the risk associated with the

presence of only $\epsilon 4$ allele or only low reserve. This is in contrast to a multiplicative interaction, which would quantify the extent to which the effect of both low reserve and $\epsilon 4$ -positivity would exceed the product of their separate effects. It has been suggested in epidemiological literature that additive interactions are preferable to multiplicative interactions due to their greater public health relevance.²⁸ Some have also argued that additive interactions may be more in line with the biological notion of synergism.^{29,30}

Previous literature on the interplay between cognitive reserve and genetic predisposition to dementia has reported conflicting findings. Some have found that protection against dementia as a result of physical leisure activities was more pronounced in $\epsilon 4$ carriers than in noncarriers,¹⁰ whereas others have reported the opposite pattern, with physical leisure favoring the noncarriers more.¹¹ This is in accordance with another study of physical leisure that reported a tendency for an additive interaction between physical activity and *APOE- $\epsilon 4$* status, although only for Alzheimer disease.³¹ When it comes to factors other than physical engagement, a multicenter study has found that dementia risk was halved in $\epsilon 4$ carriers with >7 years of schooling.¹² Another study, examining education, vascular risk factors, and leisure activities separately, has reported comparable magnitudes of dementia risk reduction among both carriers and noncarriers of *APOE- $\epsilon 4$* in the presence of optimal levels of modifiable risk factors,¹³ which was also in accordance with our results. An imaging study has shown that higher educated $\epsilon 4$ carriers exhibited similar levels of metabolism in medial temporal and prefrontal areas as the noncarriers,³² suggesting that stimulating environments could help postpone cognitive changes in carriers of genetic risk for dementia. Another study has examined the contribution of behavioral, reserve-stimulating, and cardiometabolic factors to the rate of cognitive ageing in black and white *APOE- $\epsilon 4$* carriers and reported that a number of factors were able to provide resilience against cognitive ageing (measured by MMSE) even in $\epsilon 4$ -positive subjects.³³

It may appear counterintuitive that we simultaneously found identical risks of dementia in both *APOE- $\epsilon 4$* carriers and noncarriers with higher cognitive reserve (suggesting independence between the factors), as well as an additive interaction between reserve and *APOE- $\epsilon 4$* status (suggesting a synergistic relationship between reserve and genetic predisposition). Reconciling the 2 findings is possible once the hazards of dementia in the 2 *APOE- $\epsilon 4$* subgroups with low reserve are compared. The HRs are nonoverlapping, and the $\epsilon 4$ -positive group with low reserve has a higher risk of dementia than the $\epsilon 4$ -negative subgroup with low reserve. It is precisely this difference that gives rise to the additive interaction reported here. At the same time, the HRs overlap

across *APOE- $\epsilon 4$* status once the low scores on reserve are avoided, with the risk estimates becoming virtually identical in the high reserve subgroup. These 2 distinct, yet equally important findings—(1) excess dementia risk in the face of low reserve and $\epsilon 4$ -positivity; and (2) similarly lowered risk of dementia in the face of high reserve irrespective of *APOE- $\epsilon 4$* status—are the key pieces of new evidence generated by this study on the interplay between cognitive reserve and genetic risk for dementia. These findings are especially timely, given that a recent study examining the interaction between the *APOE* genotype and other genetic risk factors concluded that dementia risk of $\epsilon 4$ carriers was most receptive to modification.³⁴ Accordingly, it has been argued that identifying resources that improve cognitive reserve should be a priority for patients with high genetic risk.³⁵ Our findings suggest that a cognitive reserve indicator comprising several activities could be one such resource.

Strengths of this study include a prospective cohort design with a relatively long follow-up period. Dementia diagnosis was reliably ascertained in a clinical setting following a comprehensive 3-step assessment. Limitations include the difficulty of timing dementia given the interexamination time gaps of 3 (or 6) years. For individuals who died during this period, linkages to hospitalization and cause-of-death registers were available to determine dementia status at death. In ascertaining dementia status among the deceased participants, SNAC-K physicians do not just accept the diagnoses listed on medical/cause of death records. Instead, they consult full medical charts, allowing them to independently determine participants' dementia status. This allows for better precision of diagnosing dementia in deceased participants. Nonetheless, we accept that some underestimation of dementia cases among the deceased during the interexamination window may have occurred. Reverse causality between preclinical dementia and self-reported exposure information at baseline could have occurred. To help reduce it, we restricted the study to cognitively intact dementia-free participants at baseline and conducted sensitivity analyses where incident cases during the first follow-up were excluded. Information on observed contributors to cognitive reserve was self-reported, potentially increasing measurement error. Our usage of an SEM-based latent variable approach allowed for the correction of unreliability in observed factors by attenuating measurement error. Nonresponse bias may have occurred, although the proportion of dropouts due to refusals was low, and those excluded were older and frailer than the analyzed population, suggesting effect underestimation. In sensitivity analyses, multiple imputation produced estimates similar to the complete-case analysis. The rate of dementia occurrence in our study population was arguably lower than expected. One

possibility is the restriction of the study sample to cognitively intact baseline participants who were not in the pre-clinical stage of dementia. Additionally, the positive selectivity of the study population (more fit and of higher socioeconomic status), a recent decline in dementia occurrence observed in Sweden and internationally,³⁶ and the low sensitivity of diagnoses among deceased participants could have lowered the rate of dementia occurrence here.

In conclusion, we found that when 4 reserve-enhancing factors from distinct periods during the life course—early life education, midlife substantive work complexity, and late life social network and leisure activities—were combined into a reserve indicator, a reduced risk of dementia in late life was demonstrated. The risk-reducing effects of the reserve indicator were such that it largely negated the effects of a genetic predisposition to dementia. These findings underscore the clinical relevance of interventions aimed at comprehensively enhancing cognitive reserve throughout life, which might be an especially viable preventive strategy in at-risk subpopulations genetically predisposed to dementia.

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Author Contributions

S.D., A.M., W.X., A.D.-M., and L.F. contributed to the conception and design of the study. All authors contributed to the acquisition and analysis of the data. S.D. and A.M. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

Nothing to report.

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