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The Influence of Birth Cohorts on Future Cognitive Decline

Valérie Turcotte[a,b], Carol Hudon[a,b,c], Olivier Potvin[b], Mahsa Dadar[d] and Simon Duchesne[b,e,*] for the Alzheimer's Disease Neuroimaging Initiative[1]

[a]*École de Psychologie, Faculté des Sciences Sociales, Université Laval, Québec, QC, Canada*
[b]*CERVO Brain Research Centre, Centre Intégré Universitaire en Santé et Services Sociaux de la Capitale Nationale, Québec, QC, Canada*
[c]*VITAM – Centre de Recherche en Santé Durable, Centre Intégré Universitaire en Santé et Services Sociaux de la Capitale Nationale, Québec, QC, Canada*
[d]*Department of Psychiatry, Faculty of Medicine, McGill University, Montréal, QC, Canada*
[e]*Département de Radiologie et Médecine Nucléaire, Faculté de Médecine, Université Laval, Québec, QC, Canada*

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Abstract.
Background: Slowed rates of cognitive decline have been reported in individuals with higher cognitive reserve (CR), but interindividual discrepancies remain unexplained. Few studies have reported a birth cohort effect, favoring later-born individuals, but these studies remain scarce.
Objective: We aimed to predict cognitive decline in older adults using birth cohorts and CR.
Methods: Within the Alzheimer's Disease Neuroimaging Initiative, 1,041 dementia-free participants were assessed on four cognitive domains (verbal episodic memory; language and semantic memory; attention; executive functions) at each follow-up visit up to 14 years. Four birth cohorts were formed according to the major historical events of the 20th century (1916–1928; 1929–1938; 1939–1945; 1946–1962). CR was operationalized by merging education, complexity of occupation, and verbal IQ. We used linear mixed-effect models to evaluate the effects of CR and birth cohorts on rate of performance change over time. Age at baseline, baseline structural brain health (total brain and total white matter hyperintensities volumes), and baseline vascular risk factors burden were used as covariates.
Results: CR was only associated with slower decline in verbal episodic memory. However, more recent birth cohorts predicted slower annual cognitive decline in all domains, except for executive functions. This effect increased as the birth cohort became more recent.
Conclusion: We found that both CR and birth cohorts influence future cognitive decline, which has strong public policy implications.

Keywords: Aging, birth cohorts, cognitive decline, cognitive reserve, generations, neuropsychology

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

*Correspondence to: Simon Duchesne, PhD, Département de Radiologie et Médecine Nucléaire, Université Laval, 1050 avenue de la Médecine, Québec, QC, G1V 0A6, Canada. Tel.: +1 418 663 5741/Ext. 24777; E-mail: simon.duchesne@fmed.ulaval.ca.

INTRODUCTION

Cognitive decline is subtended by multiple factors affecting overall brain health, such as tissue atrophy [1], cerebrovascular lesions (e.g., white matter hyperintensities, WMH) [2], and cardiovascular risk factors such as smoking, late-life type 2 diabetes, midlife hypertension, and obesity [3]. However, these factors alone cannot sufficiently predict whether an individual will experience a trajectory of normal or pathological (e.g., Alzheimer's disease, AD) cognitive aging. To explain this disparity, cognitive reserve (CR) has been proposed as a mechanism by which an individual's cognitive processes can cope with neurological changes induced by normal or pathological aging, allowing them to compensate longer for cognitive impairment [4, 5]. Reduced risk of dementia has been reported among individuals with higher education [6, 7], greater occupational complexity in adulthood [8, 9], or higher verbal intellectual quotient (IQ) [10], all of which are used as proxies of CR. Although there is evidence for beneficial effects of a higher CR on delaying the onset of dementia, previous findings remain inconsistent regarding its association with trajectories of cognitive decline [11].

There are possible explanations for these discrepancies. First, results across studies may depend on heterogeneity in the operationalization of CR [12, 13] or in the tests used to assess cognitive decline in various domains. Second, results may vary according to the birth cohort into which individuals were born [14]. Birth cohorts encompass a societal context that varies with major historical events (e.g., Great Depression, World War II) and in which individuals do not experience the same opportunities in at least their formative years. Several studies have reported differences between birth cohorts in cognitive performances and rates of age-associated cognitive decline, most often favoring individuals born in more recent cohorts [15–20]. In a previous study, we showed that when comparing birth cohorts cross-sectionally, there was an association between improved CR proxies in more recent birth cohorts and better cognitive performance [21]. These later-born individuals may have benefited from the societal changes in which CR proxies are embedded [15, 22] and thus may have had lasting effects on their brain development [23] and cognitive function [22]. However, differences between studies remain as birth cohorts are not operationalized in similar ways [21]. Although some studies included only age as a covariate [24], most controlled for additional individual characteristics such as sex [15–17, 19, 20, 25], education [15–20, 25], occupational complexity [15], or the presence of chronic diseases [16, 17, 20]. Nevertheless, studies of birth cohorts in cognitive decline remain scarce. To our knowledge, no studies have investigated the influence of birth cohorts and CR longitudinally while controlling for factors such as brain health and cardiovascular risk.

Study aims and hypotheses

Our aim was to assess the association between baseline CR, birth cohorts (year of birth), and cognitive decline in a well characterized North American cohort, the Alzheimer's Disease Neuroimaging Initiative (ADNI), controlling for demographics (age at baseline, sex), brain health, and cardiovascular risk. We operationalized birth cohorts as being defined by major historical events in the first half of the 20th century. We hypothesized that individuals with higher CR or from more recent birth cohorts ($\geq$1939) would show slower annual cognitive decline in all cognitive domains compared to those with lower CR or born earlier. Because of sociocultural conditions in North America in the early 20th century and correspondingly expected lower CR, we hypothesized that women would experience greater decline than men in all birth cohorts. We further posited that healthier brain structure (higher brain volume and lower WMH burden), and less vascular risk factors at baseline would predict a slower cognitive decline in all domains.

METHODS

Ethics approval

Approval from the local ethics board (CIUSSS-CN #2021-2054) was obtained to perform this study. Participants' written informed consent were obtained as part of the ADNI study.

Participants and birth cohorts

We obtained data from the ADNI database in May 2021. ADNI was launched in 2003 as a public-private partnership and led by Principal Investigator Michael W. Weiner, MD. Its primary goal is to test whether serial magnetic resonance imaging (MRI), positron emission tomography, other biological markers, and clinical and neuropsychological

assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD [26]. Participants were recruited through 67 sites in Canada and the United States, ranged in age from 55 to 90 years, were fluent in English or Spanish, and had completed at least six years of education. Participants underwent a series of initial tests that were repeated at intervals over subsequent years, including a clinical evaluation, neuropsychological tests, and MRI (http://adni.loni.usc.edu/) [26]. We included only participants without dementia (i.e., with normal cognition [NC] or MCI), with available baseline MRI data and at least two follow-up cognitive evaluations. Demographics were obtained at baseline, including sex (women or men), ethnicity, year of birth, education, and main occupational attainment.

Following our previous study design in Turcotte et al. [21], four birth cohorts were formed based on major historical events that happened in the United States and Canada in the 20th century [14], namely: World War I, Spanish influenza pandemic and pre-Great Depression ($\leq$1928); Great Depression (1929 to 1938); World War II (1939 to 1945); and post-World War II and Baby boom ($\geq$1946) [21].

Primary measures

Neuropsychological assessments and cognitive decline

At baseline and each follow-up visit, cognitive performance was assessed using 10 neuropsychological tests (paper-and-pen), representing four cognitive domains (Table 1). As in our previous study [21], we created a composite score by averaging the test z-scores (based on the mean and standard deviation of the present study sample) for each the following cognitive domains: language and semantic memory, attention capacities, and executive functions. Completion times of the Trail Making Test (TMT) were reverse coded for interpretation (i.e., higher score can be interpreted as better performance for all tests), and TMT B/A time ratio was inversed and reflected before calculating z-scores due to a severe negatively skewed distribution [21]. A composite z-score for verbal episodic memory was created using the Crane et al. [27] composite z-score, which was recalculated according for the mean and standard deviation of the study sample [21]. The latter [27] was used because it accounts for the difference in difficulty between the two versions administered in ADNI of the Rey Auditory Verbal Learning Test [27].

Cognitive reserve assessment

A baseline CR score was created by summing scores (0, 1 or 2) of three validated CR proxies, each with equal weight (range 0 to 6, with higher scores indicating greater CR) [21]. First, years of education were categorized based on the American education system, as previously done [21, 28, 29], where $\leq$12 years (high school and lower) were coded as 0, between 13–16 years (college and undergraduate programs) as 1, and $\geq$17 years (graduate programs and higher) as 2 [21]. Second, verbal IQ was estimated by transforming the number of errors made in the American version of the National Adult Reading Test [30] using the formula of Grober and Sliwinski [31], as previously done [21, 32]. It was categorized based on standard IQ mean and standard deviation (M = 100, SD = 15) [33], where estimates $\leq$115 (average: –1 to 1 SD) were coded as 0, between 116–123 (above average: 1 to 1.5 SD) as 1 and $\geq$124 (high above average: >1.5 SD) as 2 [21]. Finally, the complexity of main occupational attainment during adulthood was scored by three independent raters (VT and two others; averaged kappa = 0.716: substantial agreement [34]) using the 10 groups of the International Standard Classification of Occupations 2008 (ISCO-08; Supplementary Table 1) [35], as previously published [21, 36]. The major groups were classified based on the skill levels of the ISCO-08 (from 1 to 4, with higher score indicating a greater skill level), where groups 1 and 2 (skill level 4) were coded as 2, group 3 (skill level 3) as 1 and groups 4 to 10 (skill levels 1 and 2) as 0 [21].

Covariate measures

Brain health measures

As we previously did [21], brain health was assessed via imaging proxies, that is total brain and total WMH volumes at baseline. Structural brain measurements were obtained using a standardized 3D volumetric T1-weighted acquisition on either 1.5 or 3 Tesla MRI (General Electric Healthcare, Philips Medical Systems or Siemens Medical Solutions) [37]. Following the procedure defined in Potvin, et al. [38], the "recon-all -all" command of *FreeSurfer* 6.0 [39] was used on the raw images with the fully automated directive parameters (no manual intervention or expert flag options) on the CBRAIN platform [40] in order to derive the total brain volumes from these T1-weighted images. Since ADNI did not include FLAIR until 2010, we used, as in our previous study [21], a validated segmentation technique to

Table 1
Neuropsychological tests and the scores used for cognitive domains

Cognitive domain	Neuropsychological test and score used
Verbal episodic memory	• Mini-Mental State Examination: Three words delayed recall • Logical Memory I and II of the Wechsler Memory Scale: Number of elements correctly recalled for story A, immediate and delayed conditions • Rey Auditory Verbal Learning Test: 15 words recalled in five learning trials, after interference list and after delay • Word recall, Delayed free recall, and Word recognition subtests of the ADAS-Cog
Language and Semantic memory	• Naming Objects and Fingers subtest of the ADAS-Cog: Number of objects (total = 12) and fingers (total = 5) named • Semantic Verbal Fluency Test: Number of animals named in one minute
Attention capacities	• Trail Making Test: Part A time (150 secs maximum) • Number Cancellation subtest of the ADAS-Cog: Number of target hits (total = 49)
Executive functions*	• Trail Making Test: Part B time / Part A time ratio (300 secs maximum for Part B)

*B/A time ratio reduces the influence of speed and isolate the additional time associated to the task switching cost of Part B [51]. ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive.

automatically segment total WMH volumes from T1-weighted images using a set of spatial and intensity features, and a Random Forest classifier [41]. WMH are defined as areas of higher signal than the surrounding normal-appearing white matter, reflecting demyelination and axonal loss. WMH volumes from FLAIR and T1-weighted have high correlations in all brain regions ($r = 0.96$) [41]. Raw WMH volumes were log-transformed to obtain normal distribution.

Vascular risk factor burden

We calculated a vascular index score at baseline by summing the scores of four vascular risk factors (each coded as 1 = present or 0 = absent), as previously published [21, 42, 43]. The vascular index was multiplied by –1, ranging from 0 to –4, with lower negative scores indicating a higher burden of vascular risk factors [21]. We included type 2 diabetes (fasting plasma glucose $\geq$ 126 mg/dL [44]), hypertension (high systolic $\geq$130 mm Hg or diastolic $\geq$80 mm Hg [45]), obesity (body mass index $\geq$30 kg/m^2 [46]) and lifetime smoking history (past or current smoker). Missing data in vascular risk factors were coded as 0 (absent) [21].

Statistical analyses

All predicted variables were transformed into z-scores. Birth cohorts' differences were examined with one-way ANOVAs for continuous variables and with Kruskal-Wallis for categorical variables. We used linear mixed-effect models (LMMs) fit by maximum likelihood to evaluate the effects of CR and birth cohorts on rate of performance change in four cognitive domains over time. We included time (years of follow-up, as continuous variable), age at baseline (years), birth cohorts, baseline CR score, baseline total brain volume (with positive z-score meaning higher brain volume), baseline total WMH volume (with negative z-scores meaning lower WMH burden), and baseline vascular index, as well as their interactions with time (except for time), as fixed effects. As previously published [21], dummy coding was applied to birth cohorts with the earliest birth cohort (1916 to 1928) as the reference. A random intercept for participant ID and a random slope for time were included to account for within-subject correlations and for subject-specific slopes over time. Inspection of the residuals and random-effect coefficients was done to ensure that the LMM assumptions were met. The random intercept and random slope were correlated in the models. All analyses and figures were performed in RStudio (v1.3.1093; significance set at $p < 0.05$) [47] with the R packages lme4, ggplot2, and ggpubr. The R syntax of the LMMs is displayed in the Supplementary Material.

RESULTS

Participants characteristics

Baseline participant characteristics are shown in Table 2. The study sample comprised 1,041 older adults (474 women; 93.0% white; $n = 445$ with NC; $n = 596$ with MCI) with the 1929–1938 cohort having the largest number of participants ($n = 446$; 42.8%).

Table 2
Baseline characteristics* of participants by birth cohorts

Variables	All	Birth Cohorts				p
		1916–1928 World War I, Spanish influenza, pre-Great Depression	1929–1938 Great Depression	1939–1945 World War II	1946–1962 Post-World War II, Baby boom	
n (%)	1,041 (100%)	227 (21.8%)	446 (42.8%)	206 (19.8%)	162 (15.6%)	
Follow-up time (y)	4.6 (3.2)	4.8 (3.3)	5.0 (3.4)	4.3 (2.8)	3.3 (2.4)	****
Age (y)	73.6 (6.9)	82.0 (3.1)	74.9 (3.6)	69.3 (4.1)	64.1 (4.3)	****
Year of birth	1936 (8.7)	1925 (2.9)	1934 (2.7)	1942 (2.0)	1950 (3.4)	
Sex (women)	474 (45.5%)	83 (36.6%)	192 (43.0%)	108 (52.4%)	91 (56.2%)	****
Mini-Mental State Examination	28.1 (1.8)	27.7 (1.9)	28.1 (1.8)	28.4 (1.6)	28.6 (1.6)	****
Diagnostic						0.122
Normal cognition	445 (42.7%)	84 (37.0%)	203 (45.5%)	83 (40.3%)	75 (46.3%)	
Mild cognitive impairment	596 (57.3%)	143 (63.0%)	243 (54.5%)	123 (59.7%)	87 (53.7%)	
Cognitive reserve score	3.6 (1.9)	3.5 (1.9)	3.6 (1.8)	3.4 (1.9)	4.0 (1.8)	**0.009**
Education (y)	16.2 (2.8)	16.0 (3.1)	16.2 (2.7)	16.0 (2.7)	16.7 (2.5)	**0.034**
0: High school and lower, ≤ 12	137 (13.2%)	33 (14.5%)	57 (12.8%)	33 (16.0%)	14 (8.6%)	
1: College and undergraduate, 13–16	447 (42.9%)	100 (44.1%)	195 (43.7%)	86 (41.7%)	66 (40.7%)	
2: Graduate and higher, ≥17	457 (43.9%)	94 (41.4%)	194 (43.5%)	87 (42.2%)	82 (50.6%)	
Verbal IQ (estimate)	118.2 (9.3)	118.3 (9.5)	117.8 (9.4)	117.7 (9.1)	119.9 (8.6)	0.091
0: Average, ≤115	350 (33.6%)	77 (33.9%)	158 (35.4%)	73 (35.4%)	42 (25.9%)	
1: Above average, 116–123	374 (35.9%)	78 (34.4%)	159 (35.7%)	77 (37.4%)	60 (37.0%)	
2: High above average, ≥124	317 (30.5%)	72 (31.7%)	129 (28.9%)	56 (27.2%)	60 (37.0%)	
Complexity of occupation (ISCO-08)						**0.002**
0: Skill levels 1-2, groups 4–10	265 (25.5%)	64 (28.2%)	105 (23.5%)	65 (31.6%)	31 (19.1%)	
1: Skill level 3, group 3	148 (14.2%)	36 (15.9%)	57 (12.8%)	35 (17.0%)	20 (12.3%)	
2: Skill level 4, groups 1-2	628 (60.3%)	127 (55.9%)	284 (63.7%)	106 (51.5%)	111 (68.5%)	
Vascular index†	–1.3 (0.9)	–1.4 (0.8)	–1.3 (0.9)	–1.2 (0.9)	–1.4 (1.0)	0.133
Hypertension	679 (65.2%)	157 (69.2%)	303 (67.9%)	124 (60.2%)	95 (58.6%)	**0.032**
Obesity	202 (19.4%)	40 (17.6%)	75 (16.8%)	42 (20.4%)	45 (27.8%)	**0.021**
Type 2 diabetes‡	70 (6.7%)	22 (9.7%)	33 (7.4%)	8 (3.9%)	7 (4.3%)	0.412
Ever smoked§	372 (35.7%)	91 (40.1%)	176 (39.5%)	65 (31.6%)	40 (24.7%)	0.803
Structural brain measures (Z score)						
Total brain volume	0.0 (1.0)	–0.7 (0.8)	–0.2 (0.9)	0.5 (0.9)	0.9 (0.8)	****
Total WMH volume¶	0.0 (1.0)	0.6 (1.1)	0.1 (1.0)	–0.3 (0.8)	–0.6 (0.6)	****
Cognitive performances (Z score)						
Verbal episodic memory	0.0 (0.8)	–0.2 (0.7)	–0.0 (0.8)	0.2 (0.8)	0.3 (0.8)	****
Language and semantic memory	0.0 (0.7)	–0.2 (0.7)	–0.0 (0.7)	0.1 (0.6)	0.4 (0.5)	****
Attention capacities	0.1 (0.8)	–0.3 (0.8)	0.1 (0.7)	0.3 (0.7)	0.4 (0.7)	****
Executive functions	0.1 (1.0)	–0.0 (1.0)	0.1 (1.0)	0.1 (1.0)	0.3 (0.9)	**0.004**

****$p < 0.0001$. Of the 1,041 participants, 541 were from ADNI1, 29 from ADNIGO, 352 from ADNI2, and 119 from ADNI3. *Values shown are mean (standard deviation) or number (percentage). †215 missing values. ‡215 missing values. §119 missing values. ¶Negative Z scores mean lower WMH burden. IQ, intellectual quotient; ISCO-08, International Standard Classification of Occupations 2008; WMH, white matter hyperintensities.

A large proportion of participants achieved a high educational level (43.9% had ≥17 years), had verbal IQ estimates well above average (30.5% had estimates ≥124), and held more complex jobs (60.3% classified in the ISCO-08's groups 1 and 2; Supplementary Table 1). The average follow-up time was 4.6 years (range 0.5–14.0), accounting for 6230 observations across all follow-ups. The 1929–1938 cohort showed the highest average follow-up time (M = 5.0 years), followed by the 1916–1928 cohort (M = 4.8 years).

Cognitive performance

Time ($p < 0.0001$), except for executive functions, and higher CR ($p < 0.0001$) were respectively associated with worse and better performances for all cognitive domains (Table 3; see Supplementary Table 2 for effect sizes). Higher age at baseline ($p = 0.004$) was associated with better performance only in verbal episodic memory. Healthier brains at baseline were related to better cognitive performances as indicated by total

Table 3
Linear mixed effects models for variables predicting annual decline in cognitive performance in four domains (N = 1041)

	Verbal episodic memory (z)				Language and semantic memory (z)				Attention capacities (z)				Executive functions (z)			
Predictors	*B (SE)*	*Std. B*	*95% CI*	*p*	*B (SE)*	*Std. B*	*95% CI*	*p*	*B (SE)*	*Std. B*	*95% CI*	*p*	*B (SE)*	*Std. B*	*95% CI*	*p*
(Intercept)	–1.97 (0.57)	–0.39 (0.09)	–3.08—0.86	****	–0.50 (0.42)	–0.34 (0.09)	–1.32–0.32	0.231	0.32 (0.47)	–0.33 (0.09)	–0.60–1.25	0.495	–0.86 (0.53)	–0.12 (0.07)	–1.91–0.19	0.108
Time (years since baseline)	–0.59 (0.11)	–0.36 (0.04)	–0.82—0.37	****	–0.54 (0.13)	–0.36 (0.06)	–0.79—0.29	****	–0.82 (0.14)	–0.43 (0.06)	–1.10—0.54	****	–0.19 (0.13)	–0.15 (0.04)	–0.44–0.05	0.124
Age at baseline	0.02 (0.01)	0.24 (0.06)	0.01–0.03	**0.004**	0.00 (0.01)	0.15 (0.06)	–0.01–0.01	0.680	–0.01 (0.01)	0.13 (0.06)	–0.02–0.01	0.298	0.01 (0.01)	0.07 (0.04)	–0.01–0.02	0.301
CR*	0.12 (0.01)	0.25 (0.03)	0.09–0.14	****	0.10 (0.01)	0.25 (0.03)	0.08–0.12	****	0.06 (0.01)	0.15 (0.03)	0.04–0.08	****	0.09 (0.01)	0.20 (0.02)	0.07–0.12	****
Birth cohorts†																
1929–1938	0.15 (0.08)	0.23 (0.10)	–0.01–0.30	0.068	0.03 (0.06)	0.16 (0.10)	–0.08–0.15	0.573	0.07 (0.07)	0.20 (0.10)	–0.06–0.20	0.264	0.06 (0.07)	0.10 (0.07)	–0.08–0.21	0.410
1939–1945	0.35 (0.12)	0.54 (0.14)	0.13–0.58	**0.002**	0.19 (0.09)	0.47 (0.14)	0.02–0.35	**0.030**	0.10 (0.10)	0.33 (0.14)	–0.09–0.29	0.297	0.03 (0.11)	0.16 (0.10)	–0.18–0.25	0.758
1946–1962	0.36 (0.15)	0.69 (0.18)	0.07–0.64	**0.015**	0.27 (0.11)	0.64 (0.18)	0.06–0.49	**0.012**	0.03 (0.12)	0.39 (0.18)	–0.21–0.27	0.781	0.14 (0.14)	0.21 (0.13)	–0.13–0.42	0.314
Vascular index‡	–0.00 (0.03)	–0.02 (0.03)	–0.06–0.05	0.934	0.01 (0.02)	–0.02 (0.03)	–0.03–0.05	0.642	0.03 (0.02)	0.00 (0.03)	–0.02–0.07	0.260	–0.03 (0.03)	–0.02 (0.02)	–0.08–0.02	0.305
Tot. brain volume	0.22 (0.03)	0.33 (0.03)	0.16–0.27	****	0.08 (0.02)	0.23 (0.03)	0.03–0.12	****	0.18 (0.02)	0.38 (0.03)	0.13–0.23	****	0.11 (0.03)	0.12 (0.02)	0.06–0.17	****
Tot. WMH volume	–0.09 (0.03)	–0.13 (0.03)	–0.15—0.04	**0.001**	–0.04 (0.02)	–0.11 (0.03)	–0.08–0.00	0.066	–0.07 (0.02)	–0.14 (0.03)	–0.11—0.02	**0.003**	–0.07 (0.03)	–0.08 (0.02)	–0.12—0.02	**0.007**
Time × Age at baseline	0.01 (0.00)	0.11 (0.03)	0.00–0.01	****	0.01 (0.00)	0.14 (0.04)	0.00–0.01	****	0.01 (0.00)	0.19 (0.04)	0.01–0.01	****	0.00 (0.00)	0.03 (0.03)	–0.00–0.00	0.281
Time × CR	0.01 (0.00)	0.03 (0.01)	0.00–0.01	**0.026**	0.00 (0.00)	0.01 (0.02)	–0.00–0.01	0.673	0.00 (0.00)	0.02 (0.02)	–0.00–0.01	0.257	0.00 (0.00)	0.02 (0.01)	–0.00–0.01	0.073
Time × 1929–1938	0.03 (0.02)	0.08 (0.04)	0.00–0.06	**0.042**	0.03 (0.02)	0.12 (0.06)	0.00–0.07	**0.047**	0.04 (0.02)	0.13 (0.06)	0.00–0.08	**0.035**	0.02 (0.02)	0.04 (0.04)	–0.02–0.05	0.329
Time × 1939–1945	0.08 (0.02)	0.21 (0.06)	0.03–0.12	**0.001**	0.07 (0.03)	0.24 (0.09)	0.02–0.12	**0.010**	0.07 (0.03)	0.23 (0.09)	0.02–0.13	**0.012**	0.05 (0.03)	0.13 (0.07)	–0.00–0.10	0.069
Time × 1946–1962	0.13 (0.03)	0.35 (0.08)	0.07–0.19	****	0.08 (0.03)	0.30 (0.13)	0.01–0.15	**0.017**	0.12 (0.04)	0.37 (0.12)	0.04–0.19	**0.002**	0.03 (0.03)	0.07 (0.10)	–0.04–0.09	0.460
Time × Vascular index	–0.01 (0.00)	–0.02 (0.01)	–0.02–0.00	0.094	–0.01 (0.01)	–0.04 (0.02)	–0.02—0.00	**0.035**	–0.01 (0.01)	–0.02 (0.02)	–0.02–0.00	0.174	–0.00 (0.01)	–0.00 (0.01)	–0.01–0.01	0.999
Time × Tot. brain volume	0.04 (0.01)	0.12 (0.01)	0.03–0.06	****	0.04 (0.01)	0.14 (0.02)	0.03–0.05	****	0.06 (0.01)	0.18 (0.02)	0.04–0.07	****	0.00 (0.01)	0.00 (0.02)	–0.01–0.01	0.826
Time × Tot. WMH volume	–0.02 (0.01)	–0.04 (0.01)	–0.03—0.01	**0.002**	–0.02 (0.01)	–0.07 (0.02)	–0.03—0.01	**0.001**	–0.02 (0.01)	–0.06 (0.02)	–0.03—0.01	**0.001**	–0.00 (0.01)	–0.01 (0.02)	–0.01–0.01	0.684
Random effects																
Σ^2	0.09				0.12				0.15				0.64			
τ_{00}	0.58 $_{\text{ParticipantID}}$				0.29 $_{\text{ParticipantID}}$				0.36 $_{\text{ParticipantID}}$				0.32 $_{\text{ParticipantID}}$			
τ_{11}	0.01 $_{\text{ParticipantID.Time}}$				0.01 $_{\text{ParticipantID.Time}}$				0.02 $_{\text{ParticipantID.Time}}$				0.00 $_{\text{ParticipantID.Time}}$			
τ_{01}	0.42 $_{\text{ParticipantID}}$				0.30 $_{\text{ParticipantID}}$				0.36 $_{\text{ParticipantID}}$				–0.11 $_{\text{ParticipantID}}$			
Marginal R^2	0.225				0.170				0.209				0.071			
Conditional R^2	0.932				0.857				0.864				0.383			

****$p < 0.0001$. 6,230 observations. Intercept, baseline performance for an individual with value zero on all predictors; slope, change over time; Marginal R^2 describes the proportion of variance explained by only the fixed factors; Conditional R^2 describes the proportion of the variance explained by both the fixed and random factors. *Cognitive reserve (CR) score at baseline, ranging from 0 (low cognitive reserve) to 6 (high cognitive reserve). †1916–1928 is the reference. 1929–1938, 1939–1945 and 1946–1962:1 = born in this cohort, 0 = born in another cohort. ‡Vascular index at baseline, ranging from 0 (no vascular risk factor burden) to –4 (high vascular risk factors burden). B, beta coefficient; SE, standard error; Std. B, standardized beta coefficient; CI, confidence interval; Tot. brain volume, total brain volume z-score at baseline; Tot. WMH volume, total white matter hyperintensities volume z-score at baseline; σ^2, residual variance (within-subject variance); τ_{00}, random intercept variance (between-subject variance); τ_{11}, random slope variance; ρ_{01}, random slope-intercept correlation.

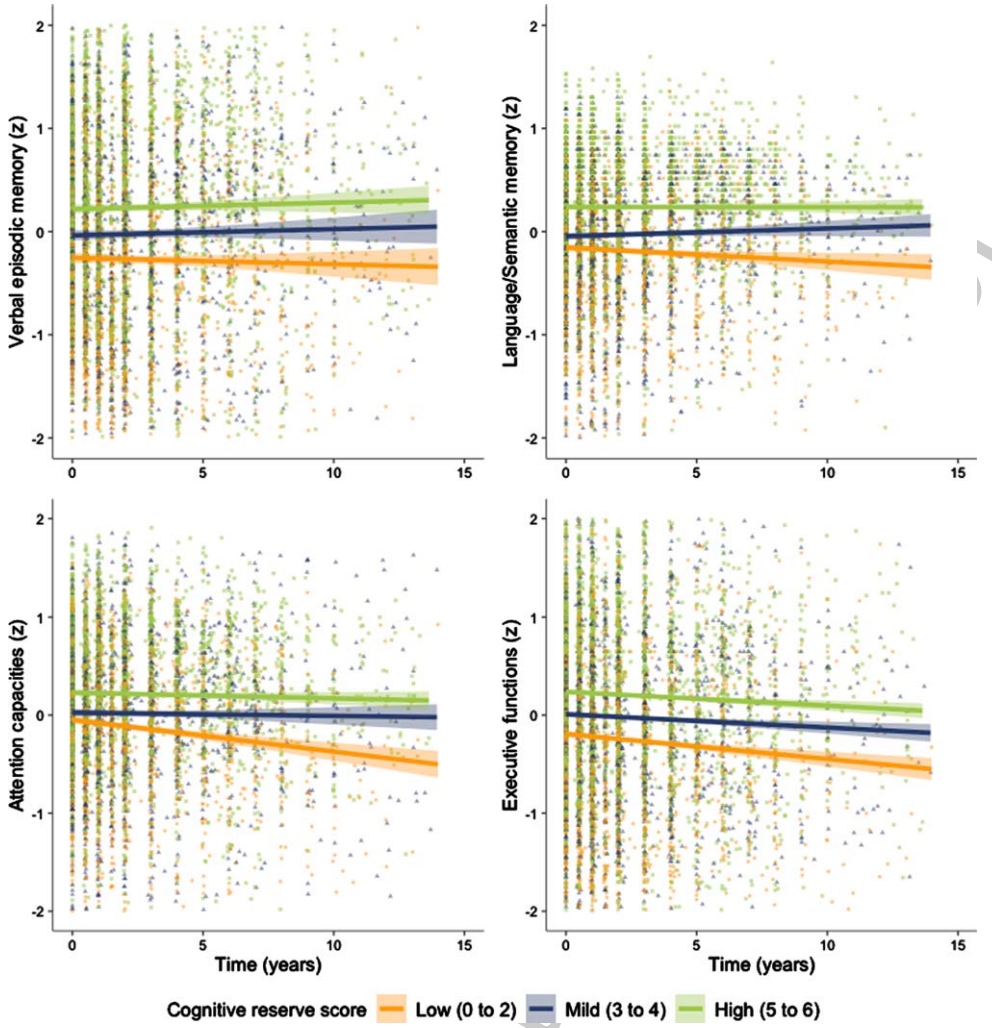

Fig. 1. Moderation effects of cognitive reserve on the association between cognitive performances in four domains and time. Note: 95% confidence intervals are shown as shaded areas around the regression lines.

brain volume (all domains, $p < 0.0001$) and WMH burden ($p \leq 0.003$; except for language and semantic memory). Finally, participants born during the two most recent birth cohorts had better performances in verbal episodic memory (1939–1945 [$p = 0.002$], 1946–1962 [$p = 0.015$]), and language and semantic memory (1939–1945 [$p = 0.030$], 1946–1962 [$p = 0.012$]) compared to the earliest cohort (1916–1928).

Cognitive decline

CR, birth cohorts, age at baseline, and baseline brain health all influenced cognitive decline as shown by their interactions with Time (Table 3; see Supplementary Table 2 for effect sizes). Higher CR ($p = 0.026$) predicted a slower annual decline in verbal episodic memory performances (Fig. 1). Compared to their earlier born counterparts (1916–1928), participants born during all more recent cohorts had a slower cognitive decline in all domains ($p \leq 0.047$; Fig. 2). The birth cohorts' effect on cognitive decline increases as the birth cohort became more recent: Cohort born between 1929–1938, 1939–1945, and 1946–1962 had an annual cognitive decline that was respectively 0.04 SD, 0.07 SD, and 0.13 SD slower than the earliest cohort (1916–1928). Cognitive decline in all domains was slowed when participants were older at baseline ($p < 0.0001$). A healthier brain structure at baseline (higher total brain volume and lower WMH burden) predicted a slower decline in all cognitive domains ($p < 0.0001$;

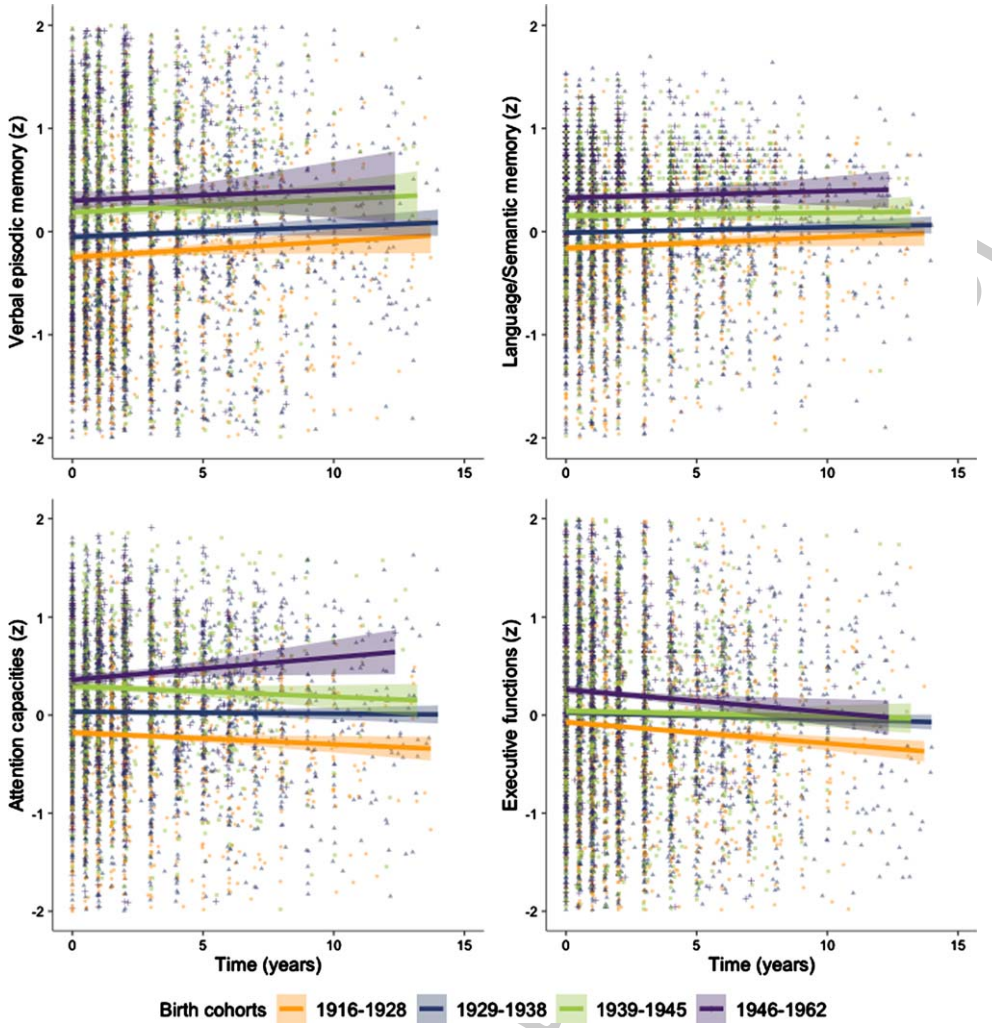

Fig. 2. Moderation effects of birth cohorts on the association between cognitive performances in four domains and time. Note: 95% confidence intervals are shown as shaded areas around the regression lines.

$p \leq 0.002$). A lower vascular index ($p = 0.035$) predicted a slower decline only in language and semantic memory performances. No variable predicted annual decline in executive functions.

sWe tested the influence of CR on birth cohorts in cognitive decline with the interaction Time × CR × Birth cohorts (0 = 1916–1938, 1 = 1939–1962), but it did not reach statistical significance in any model (Fig. 3). We also did not observe any influence of sex on cognitive decline as indicated by Time × Sex, Time × CR × Sex, and Time × Birth cohorts × Sex, neither being statistically significant. We further ran the LMMs independently for baseline diagnosis (NC and MCI; Supplementary Table 3) to explore the effects of birth cohorts and CR on longitudinal cognitive decline across diagnostic groups. Briefly, in both NC and MCI models, CR ($p \leq 0.006$, $p < 0.0001$) influenced cognitive performance in all domains, but did not reach significance level on annual decline. Being born in more recent birth cohorts slowed annual decline in verbal episodic memory (1939–1945 in MCI [$p = 0.043$] and 1946–1962 in NC [$p < 0.0001$]) and attention capacities (1946–1962 in MCI [$p = 0.021$]). In both groups, a higher baseline total brain volume predicted a slower cognitive decline in all domains ($p \leq 0.036$; except for executive functions), whereas a lower WMH burden predicted a slower decline in verbal episodic memory ($p = 0.024$), and language and semantic memory ($p = 0.031$) only in MCI. The effects of a healthier brain structure on cognitive decline were stronger in participants with MCI com-

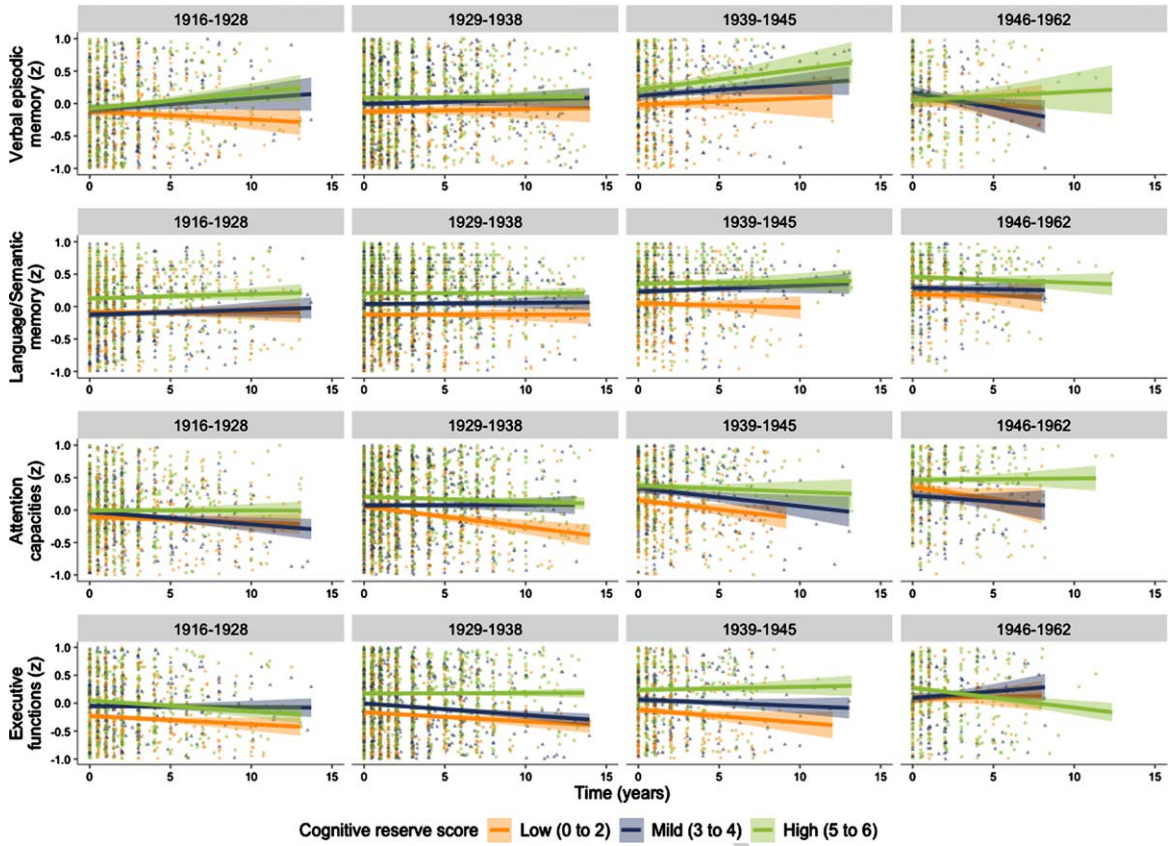

Fig. 3. Moderation effects of cognitive reserve on the association between cognitive performances in four cognitive domains and time across birth cohorts. Note: 95% confidence intervals are shown as shaded areas around the regression lines. None of the Time × CR × Birth cohort (1916–1938, 1939–1962) interactions were revealed statistically significant in the regression models.

pared to those with NC at baseline. Finally, a lower vascular index ($p = 0.036$) predicted a slower decline in language and semantic memory performance only in the MCI group.

DISCUSSION

The aim of this study was to assess the relationships between CR, birth cohorts as defined by major historical events, and cognitive decline. Our results showed that, compared to their earlier-born counterparts (1916–1928), seniors born in more recent birth cohorts exhibited a slowed annual cognitive decline in all domains, except for executive functions, and this effect increased as the birth cohort became more recent. Although higher CR predicted better performance in all cognitive domains, its effect on cognitive decline was observed only for verbal episodic memory. Cognitive decline was also reduced in individuals with healthier brain (except for executive functions) and lower vascular burden (only in language and semantic memory) at baseline. In all domains, men and women showed similar cognitive decline.

Cognitive reserve and birth cohort impacts

CR has been widely used in studies to explain heterogeneity in cognitive aging trajectories. By combining proxies of education, occupation complexity, and verbal IQ, our estimate of CR considers a wide range of experiences in both childhood and adulthood that are beneficial to individuals' cognitive functioning. However, we showed that CR fails to fully account for interindividual differences in cognitive decline. Our results suggest that societal changes in the first half of the 20th century, as defined by birth cohorts, have a significant impact on annual cognitive decline. Although secular trends have been reported for CR proxies [22], birth cohorts capture the historical context in which CR proxies are embedded, allowing for a broader and more qualitative assessment of life experiences compared to what a

quantitative score of CR can encompass. For instance, changes in the educational system have occurred, notably in the difficulty of the educational curriculum (e.g., a geometry problem saved for advanced secondary students in the 1890 s was taught to seventh graders in 1955 [48]) and in the principal modes of instruction (e.g., shift from drill and rote memorization to more participatory learning [48]), which goes beyond the assessment captured by the number of years of education.

Other factors associated with birth cohort differences may explain the difference in cognitive decline. Political and economic changes throughout the first half of the 20th century may have had different implications for cognitive development based on the individual's age during those experiences. Wars, economic crises, and pandemics have led to adverse living conditions (e.g., poor nutrition, lack of health, and social care) that may have had negative impacts on an individuals' brain development in early life. Later-born individuals might have benefited from advances in public health interventions and reduced disease burden, and therefore reach older ages in better general health [14, 49, 50].

Methodological aspects

Our findings are consistent with existing studies indicating a slower domain-specific cognitive decline favoring seniors born in more recent cohorts (e.g., verbal episodic memory [16, 18, 20]; language and semantic memory [15, 17, 19, 20]; attention capacities [19]), but are also inconsistent with other studies showing a steeper decline in these individuals (e.g., attention capacities [16, 25]), or simply no difference between birth cohorts (e.g., language and semantic memory [24, 25]; attention capacities [24]). The only cognitive domain that did not reveal evidence of birth cohort effects on annual decline was executive functions, which is contrary to previous findings both with [17] and without [15, 19] the effect of education. Although these studies mainly assessed executive functions with a phonemic verbal fluency test [15, 17], Dodge et al. [19] used the same test as ours (i.e., TMT part B), but without using the B/A time ratio to reduce the influence of speed and isolate the additional time associated with the task switching cost of part B [51]. Of the previous studies assessing language and semantic memory, only one used a task similar to ours (i.e., animals verbal fluency test [19]), whereas the others mainly used tasks involving vocabulary and lexical knowledges (i.e., forced-choice matching of a synonym to a target-word [15, 17, 24, 25], verbal reasoning task, and general knowledge task [24]), without adjusting for education [24]. While the latter tasks can provide insight into an individual's crystallized knowledge, they are much less semantically demanding than object naming or categorical verbal fluency tasks. Attention capacities were assessed using a variety of tasks involving visuo-motor (i.e., TMT part A [19]) and visuo-oral processing speed (i.e., adapted Digit Symbol [16, 24], Figure Identification [24, 25]), where the absence of a motor component led to different results from ours. It seems also likely that the use of Swedish [24, 25] or Dutch [16] versions of the cognitive tests for language and attention capacities may have contributed to contrasting results.

Moreover, disparities between these findings could result from the socio-cultural specificities regarding the countries where the studies were carried out (i.e., United States [15, 17–20], Sweden [24, 25], Netherlands [16]). Indeed, these countries have undergone different societal changes, perhaps at different times, over the last hundred years, which may have influenced the cognition of individuals. Thus, birth cohorts vary substantially across studies in terms of their quantity (i.e., from two [15–17, 20, 24] to four birth cohorts [18, 19]), the number of years covered in each cohort (i.e., from one [25] to 37 years [15]), and whether they were formed according to major historical events (e.g., before and after World War II [15]), to recruitment phases [17, 20, 24, 25] or just time (i.e., decade-long [16, 18, 19]).

Strengths and limitations

A major strength of our study is the use of ADNI data. This allowed comparison of older adults born up to 46 years apart over 14 years of follow-up on the same cognitive tests. Added to this are standardized acquisitions that allowed the estimation of brain structure health along with vascular burden across individuals. We also ensured that the influence of the sociocultural environment was well captured by forming birth cohorts based on the major historical events of the first half of the 20th century that had a major impact in North America. Thus, the combined use of multiple cognitive tests achieves a high predictive value for later cognitive decline [52] in addition to capturing intraindividual variability and subtle cognitive changes [53], which diagnostic classes cannot do. Finally, we used a combination of multiple CR

proxies, as this provides a better representation of the CR than a single proxy [12].

Some limitations must however be addressed. First, the ADNI cohort is primarily composed of highly educated, white North American individuals, which minimizes the generalizability of our results to socially disadvantaged individuals—precisely those individuals with lower CR scores. Second, a selection bias may exist because we required participants to have a minimum of two follow-ups to be included in our study. The same applies to a possible survival bias in older participants, who may have been born in earlier cohorts. For instance, this survival bias could be suggested by the finding of a statistically significant association between higher age at baseline and better cognitive performance in verbal episodic memory. Therefore, the earlier born cohorts may be more likely to represent a selective group of individuals who are less likely to show a steeper decline in comparisons to the later born cohorts. Finally, an age overlap exists between birth cohorts (Supplementary Figure 1). However, the potential effects of these age differences are minimized by the inclusion of age as a covariate in the LMMs.

Conclusion

Studies investigating birth cohort influence on cognitive decline remain scarce. We provided additional findings that support the relevance of considering the year of birth when examining cognitive decline. Our findings have strong public implications reinforcing the importance of societal programs that foster opportunities during adulthood to promote cognitive functioning in later life.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

Thedata supporting the findings of this study are openly available in ADNI database at https://adni.loni.usc.edu/ upon request: https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Data_Use_Agreement.pdf.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-220951.

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