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RESEARCH ARTICLE

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The interactive effect of demographic and clinical factors on hippocampal volume: A multicohort study on 1958 cognitively normal individuals

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Abstract

Alzheimer's disease is characterized by hippocampal atrophy. Other factors also influence the hippocampal volume, but their interactive effect has not been investigated before in cognitively healthy individuals. The aim of this study is to evaluate the interactive effect of key demographic and clinical factors on hippocampal volume, in contrast to previous studies frequently investigating these factors in a separate manner. Also, to investigate how comparable the control groups from ADNI, AIBL, and AddNeuroMed are with five population-based cohorts. In this study, 1958 participants were included (100 AddNeuroMed, 226 ADNI, 155 AIBL, 59 BRC, 295 GENIC, 279 BioFiNDER, 398 PIVUS, and 446 SNAC-K). ANOVA and random forest were used for testing between-cohort differences in demographic-clinical variables. Multiple regression was used to study the influence of demographic-clinical variables on hippocampal volume. ANCOVA was used to analyze whether between-cohort differences in demographic-clinical variables explained between-cohort differences in hippocampal volume. Age and global brain atrophy were the most important variables in explaining variability in hippocampal volume. These variables were not only important themselves but also in interaction with gender, education, MMSE, and total intracranial volume. AddNeuroMed, ADNI, and AIBL differed from the population-based cohorts in several demographic-clinical variables that had a significant effect on hippocampal volume. Variability in hippocampal volume in individuals with normal cognition is high. Differences that previously tended to be related to disease mechanisms could also be partly explained by demographic and clinical factors independent from the disease. Furthermore, cognitively normal individuals especially from ADNI and AIBL are not representative of the general population. These findings may have important implications for future research and clinical trials, translating imaging biomarkers to the general population, and validating current diagnostic criteria for Alzheimer's disease and predementia stages.

KEYWORDS
aging, Alzheimer's disease, hippocampal volume, magnetic resonance imaging, multicohort

1 | INTRODUCTION

Hippocampal atrophy has become a well-established biomarker of Alzheimer's disease (AD) (Frisoni, Fox, Jack, Scheltens, & Thompson, 2010; Morris et al., 2014). Factors such as age, gender, education, global brain atrophy, intracranial volume, and APOE ϵ4 genotype are known to influence hippocampal volume (Crivello et al., 2010; Janowitz et al., 2014; Jiang et al., 2014; Morra et al., 2009; Noble et al., 2012; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010; Shpanskaya et al., 2014; Striepens et al., 2011; Voevodskaya et al., 2014; Yamaguchi et al., 2002; Yuefeng et al., 2014). However, other studies have failed to show an effect of these factors on hippocampal volume (Janowitz et al., 2014; Jiang et al., 2014; Morra et al., 2009; Shpanskaya et al., 2014; Striepens et al., 2011; Yamaguchi et al., 2002; Yuefeng et al., 2014). An explanation for these conflicting results is that all previous studies have focused on one or a few of these factors at a time. The interactive influence of all these factors on hippocampal volume in the same study and sample has not previously been investigated.

A substantial number of the publications on hippocampal atrophy comes from three large multi-center cohorts, that is, ADNI (Mueller et al., 2005), AIBL (Ellis et al., 2010), and AddNeuroMed (Lovestone et al., 2009). However, specific recruiting procedures led to the collection of highly selected samples. In consequence, these cohorts have a higher prevalence of individuals with family history of dementia, participants are younger, more educated, and have better global cognitive status than that reported in the general population (Brodaty et al., 2014; Whitwell et al., 2012). Nonetheless, studies comparing ADNI, AIBL, and AddNeuroMed versus population-based samples are scarce and have mainly focused on the MCI and AD groups. Therefore, it is still unclear to what extent control groups from ADNI, AIBL, and AddNeuroMed are representative of the general population and whether results are generalizable.

The first aim of this study was to investigate the simultaneous effect of several demographic and clinical factors on hippocampal volume in healthy individuals. To that end, we combined eight large-scale international cohorts, leading to the largest sample to date in a study of this kind. The second aim was to investigate how comparable the control groups from ADNI, AIBL, and AddNeuroMed are with population-based cohorts. To ascertain this is critical and may have important implications, as most of the results coming from ADNI, AIBL, and

AddNeuroMed directly depend on the characteristics of the control group. A specific question was whether between-cohort differences in hippocampal volume could be successfully minimized by statistical control of key demographic and clinical factors.

2 | MATERIALS AND METHODS

2.1 | Participants

This study includes a total of 1958 cognitively normal individuals from the following eight large-scale international cohorts: AddNeuromed (http://www.innomed-addneuromed.com/, RRID:SCR_003819), ADNI (http://adni.loni.usc.edu/, RRID:SCR_003007), and AIBL (https://aibl.csiro.au/) (multicenter cohorts), and BioFINDER, BRC, GENIC, PIVUS, and SNAC-K (single-center population-based cohorts). Cohorts' characteristics and eligibility criteria are displayed in Tables 1 and 2. Approval was obtained from local ethics committees. Data collection was carried out in accordance with relevant regulations at each center and participants gave written consent in accordance with the Declaration of Helsinki.

2.2 | Demographic and clinical variables

Age, gender, education, and handedness were selected as demographic variables. Clinical information included the mini-mental state examination (MMSE), clinical dementia rating (CDR) scale, and several instruments for assessing depressive symptomatology and functional activity (Table 3). Subjective memory complaints were operationalized as detailed in Table 2. Cerebrospinal fluid (CSF) levels of $A\beta_{42}$, total tau (*T*-tau), and phosphorylated tau (*p*-tau) were also measured in ADNI and BioFINDER (Supporting Information Table 1a).

2.3 | Magnetic resonance imaging

High-resolution 3D T1-weighted sequences were acquired in all the cohorts. MRI scanner and acquisition parameters are detailed in Supporting Information Table 1b. Image processing was performed with FreeSurfer 5.1.0 (http://surfer.nmr.mgh.harvard.edu/, RRID:SCR_001847) using TheHiveDB database system (Muehlboeck, Westman, & Simmons, 2014). FreeSurfer provides measurements of cortical and subcortical volumes, as well as an estimation of the total intracranial volume (TIV) (Desikan et al., 2006; Fischl et al., 2002). Left and right hippocampal volumes were summed together. The brain volume (BV)/CSF index was also calculated as a proxy of global brain atrophy using the following formula: brain volume (BV)/CSF index = (total grey matter volume + total white matter volume)/total CSF volume. This index correlates with clinical measures, CSF biomarkers, and cognition, and has been proposed for staging individuals according to the degree of global brain atrophy and for monitoring disease progression (Orellana et al., 2016). Lower values of the BV/CSF index denote more atrophy.

2.4 | Statistical analyses

One-way independent ANOVA and ANCOVA were performed to test between-cohort differences. All *p*-values (two-sided) were adjusted using Bonferroni correction for multiple comparisons across both dependent variables and post hoc paired comparisons. The Spearman's rank correlation was used to investigate relationships between variables. Multiple linear regression was performed to analyze the influence of demographic and clinical variables on hippocampal volume. Random forest analysis and dominance analysis were performed to investigate the importance of the demographic and clinical variables in explaining differences between cohorts as well as variability in hippocampal volume, respectively (Breiman, 2001; Grömping, 2007; Liaw & Wiener, 2002). Importance is reported as *i* and reflects the relative error in classification when a predictor is excluded from the model (in random forest analysis) (Breiman, 2001; Liaw & Wiener, 2002), and the relative percentage of the variance of the regression model explained by a given predictor (in dominance analysis, multiple linear regression) (Grömping, 2007). The statistical design used for each of the analyses performed is detailed in Supporting Information Table 2. Effect sizes are reported as partial eta squared (η^2_{par}) and standardized beta (β). Results were considered significant when $p \leq .05$.

3 | RESULTS

3.1 | Between-cohort differences in demographic and clinical variables

Significant between-cohort differences were found in all the studied variables (Table 3). Age, memory complaints, depressive symptoms, and the BV/CSF index showed the greatest effect sizes ($\eta^2_{par} \geq 0.30$). Random forest analysis demonstrated that age was the most important variable in explaining differences between cohorts ($i = 526.3$), followed by education level ($i = 190.4$), TIV ($i = 148.3$), the BV/CSF index ($i = 143.6$), MMSE ($i = 77.3$), and gender ($i = 64.4$). ADNI and AddNeuroMed recruited significantly older samples as compared with AIBL and most of the population-based cohorts. Both ADNI and AIBL recruited highly educated individuals, while AddNeuroMed was comparable to the population-based cohorts. BRC and GENIC showed the smallest TIV values while ADNI, BioFINDER, and PIVUS showed the largest TIV values. Finally, the BV/CSF index had higher values (i.e., less atrophy) in the cohorts AIBL, GENIC, and SNAC-K. Lower values of the BV/CSF index (i.e., more atrophy) were observed in AddNeuroMed and PIVUS.

3.2 | Between-cohort differences in hippocampal volume

Hippocampal volume was significantly larger in AIBL than in AddNeuroMed and ADNI, and was comparable with that displayed by GENIC and SNAC-K. BRC and PIVUS were the cohorts with smallest hippocampal volume, and BioFINDER was in between (Table 3 and Figure 1).

TABLE 1 Description of cohorts' characteristics

	AddNeuroMed	ADNI	AIBL	BRC	GENIC	BioFINDER	PIVUS	SNAC-K
Full name	–	Alzheimer's disease neuroimaging initiative	Australian imaging biomarkers and lifestyle study	King's health partners biomedical research center for mental health dementia cohort	Group of neuropsychological studies from the Canary islands	Swedish BioFINDER study	Prospective investigation of the vasculature in Uppsala seniors	Swedish national study on aging and care in Kungsholmen
Type	Multicenter Case–control (AD, MCI, CTRL)	Multicenter Case–control (AD, MCI, CTRL)	Multicenter Case–control (AD, MCI, CTRL)	Single-center Population-based specifically including AD, MCI, and CTRL groups	Single-center Population-based specifically including MCI and CTRL groups	Single-center Population based	Single-center Population based	Single-center Population based
Country	Finland, France, Greece, Italy, Poland, and UK	USA and Canada	Australia	UK (London)	Spain (Canary Islands)	Sweden (Malmö)	Sweden (Uppsala)	Sweden (Stockholm)
Design	Prospective longitudinal	Prospective longitudinal	Prospective longitudinal	Prospective longitudinal	Prospective longitudinal	Prospective longitudinal	Prospective longitudinal	Prospective longitudinal
Period	2004–present	2003–present	2006–present	2007–present	2005–present	2009–present	2001–present	2001–present
Brief project description	Cross European study, part of the InnoMed (Innovative Medicines in Europe), funded by the European Union (FP6 and FP7), as well as members of the EFPIA. Designed to find biomarkers or tests for AD	Launched by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations. Established to develop standardized imaging techniques and biomarker procedures in AD research	Launched by the Australian CSIRO and a number of leading Australian research organizations. A study to discover which biomarkers, cognitive characteristics, and health and lifestyle factors determine subsequent development of symptomatic AD	BRC is a neuroimaging study which was designed to establish imaging markers for the earlier detection and diagnosis of AD. Data were collected at the Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London and South London and Maudsley NHS Foundation Trust. London, UK	Study from the University of La Laguna, aimed to investigate the cognitive and imaging profile associated to normal aging from the middle-age adulthood to the old age. Individuals living in the Canary Islands	Study from Lund University, aimed to investigate the preclinical stages of Alzheimer's disease and other dementia disorders. Further aims are to study midlife risk factors for future development of amyloid, tau, and vascular pathologies	Study from the University of Uppsala, aimed to investigate the predictive power of different measurements of endothelial function and arterial compliance in a random sample of 1,000 normal elderly individuals living in the community of Uppsala	Carried out by the Stockholm Gerontology Research Centre, the ARC at Karolinska Institutet and the Stockholm University, to detect the influence of lifetime genetic, environmental and biological factors on medical, psychological, and social health in late adulthood. Individuals living in the area of Kungsholmen/ Essingeöarna (Stockholm)

(*continues*)

TABLE 1 (continued)

	AddNeuroMed	ADNI	AIBL	BRC	GENIC	BioFINDER	PIVUS	SNAC-K
Recruitment procedure	Nonrelated members of the patient's families, caregiver's relatives and social centers for the elderly or GP surgeries	Advertisements in newspapers	Medial appeal and through participants' treating physicians	Nonrelated members of the patient's families, caregivers, relatives and social centers for the elderly, GP surgeries or advertisements in newspapers	Relatives and acquaintances of the research staff and students from the University of La Laguna, personnel from local schools, and through participants' GPs	Random sampling from the cardiovascular cohort of the population-based Malmö Diet and Cancer Study conducted in the city of Malmö, Sweden	Random sample of 1,000 subjects aged 70 years old at baseline and chosen from the register of community living	Random epidemiological sample
Data obtained from	Eric Westman and Andrew Simmons are part of AddNeuroMed	https://ida.loni.usc.edu, PI Michael M. Weiner	https://ida.loni.usc.edu and https://aibl.csiro.au (EoI), PI David Ames	Personal contact to PI Simon Lovestone and Andy Simmons	Personal contact to PI José Barroso	Personal contact to PI Oskar Hansson	Personal contact to PI Lars Lind	Personal contact to PI Laura Fratiglioni
Key references, other sources	Lovestone et al. (2009) www.innomed-addneuromed.com	Mueller et al. (2005) www.adni-info.org	Ellis et al. (2009) www.aibl.csiro.au	–	Ferreira et al. (2015)	www.biofinder.se	Lind et al. (2005) www.medsci.uu.se/pivus	Zhang et al. (2010) www.snac-k.se

AD = Alzheimer's disease; MCI = mild cognitive impairment; CTRL = control; UK = United Kingdom; FP = Framework Programme; EFPIA = European Federation for Pharmaceutical Industries and Associations; USA = United States of America; PI = principal investigator; CSIRO = Commonwealth Scientific Industrial and Research Organization; EoI = Expression of Interest; ARC = Aging Research Centre.

TABLE 2 Eligibility criteria

	AddNeuroMed	ADNI	AIBL	BRC	GENIC	BioFINDER	PIVUS	SNAC-K
Inclusion criteria								
Age	≥65 years	55–90 years	≥60 years	≥60 years	≥35 years	≥60 years	All individuals are 70 years old at baseline (Data at 5 years follow-up when MRI is collected is included in this study)	≥60 years
MMSE	24–30	24–30 (exceptions for subjects with <8 years of education)	24–30	24–30	24–30	28–30 (at screening visit)	–	24–30[a]
CDR	0	0	0 or 0.5	0	–	0	–	–
Depression	GDS ≤ 5	GDS ≤ 5	GDS ≤ 5	GDS ≤ 5	No clinical diagnosis of depression, no antidepressant drugs	No current clinical major depressive episode	–	No clinical diagnosis of depression (DSM-IV, ICD-10)
Cognition	Preserved cognitive and functional status	Normal education-adjusted performance in Logical Memory II (WMS-R)	Generally, normal education-adjusted performance in Logical Memory II (WMS-R), although some participants demonstrating failure were further investigated and included	Preserved cognitive and functional status	Preserved cognitive and functional status	Preserved cognitive and functional status	Normal elderly individuals	Nondemented individuals
Subjective complaints	A percentage of the participants expressed subjective concern about their memory function or thinking capacity. Subjective memory complaints were elicited by the question: "Do you have problems with memory or thinking?"	No memory complaints aside from those common to other normal subjects	A percentage of the participants expressed subjective concern about their memory function. Subjective memory complaints were elicited by the question: "Do you have difficulties with your memory?"	A percentage of the participants expressed subjective concern about their memory function or thinking capacity. Subjective memory complaints were elicited by the question: "Do you have problems with memory or thinking?"	A percentage of the participants expressed subjective concern about their cognitive functions. Subjective memory complaints were elicited by the question: "Do you have difficulties with your memory?"	No memory complaints aside from those common to other normal subjects. Subjective memory complaints were elicited by the question: "Do you have problems with memory or thinking?"	–	A percentage of the participants expressed subjective concern about their memory function. Subjective memory complaints were elicited by the question: "Do you think your memory has got worse?"

(*continues*)

TABLE 2 (continued)

	AddNeuroMed	ADNI	AIBL	BRC	GENIC	BioFINDER	PIVUS	SNAC-K
Functional activity	Absence of significant impairment in activities of daily living	Absence of significant impairment in activities of daily living	Intact social and occupational functioning	Absence of significant impairment in activities of daily living	FAQ ≤ 5	Absence of significant impairment in activities of daily living	Normal elderly subjects	Nondemented, non-institutionalized, and nondisabled
Medication	Stable medication	Stable medication	–	Stable medication	–	Stable medication	–	–
Health	Good general health	Good general health	–	Good general health	Good general health	Good general health	Vascular comorbidity and vascular risk factors are not excluded	Healthy elderly people
Exclusion criteria								
Cognitive impairment	Dementia (DSM-IV criteria), MCI	Dementia (DSM-IV criteria), MCI	Dementia (DSM-IV and ICD-10 criteria), MCI (Winblad et al., 2004)	Dementia (DSM-IV criteria), MCI	Dementia (DSM-IV criteria), MCI (Winblad et al., 2004)	Dementia (DSM-IV and ICD-10 criteria), MCI (Winblad et al., 2004)	–	Dementia (DSM-IV criteria)
Disease	Significant neurological or psychiatric illness, significant unstable systemic illness, or organ failure	Significant neurological or psychiatric illness, significant unstable systemic illness, or organ failure	Significant neurological or psychiatric illness, cancer (except basal cell skin carcinoma), symptomatic stroke, and uncontrolled diabetes	Significant neurological or psychiatric illness, significant unstable systemic illness, or organ failure	Significant neurological or psychiatric illness, significant systemic illness, or organ failure	Significant neurological or psychiatric illness, significant unstable systemic illness, or organ failure	–	Significant neurological or psychiatric illness, significant systemic illness or organ failure[b]
Medication	–	Current use of psychoactive medications or warfarin	–	–	Current use of psychoactive medications	Use of antipsychotic or sedative medications	–	–
Substance abuse	Alcohol or substance misuse	History of alcohol or substance abuse or dependence	Current regular alcohol use exceeding two standard drinks per day for women or four per day for men	Alcohol or substance misuse	History of alcohol or substance abuse or dependence	Current alcohol or substance misuse	–	Current alcohol or substance misuse[b]

ADNI = Alzheimer's Disease Neuroimaging Initiative; AIBL = Australian Imaging Biomarkers and Lifestyle study; BRC = King's Health Partners Biomedical Research Centre for Mental Health Dementia Cohort; GENIC = Group of Neuropsychological Studies from the Canary Islands; PIVUS = Prospective Investigation of the Vasculature in Uppsala Seniors; SNAC-K = Swedish National Study on Aging and Care in Kungsholmen; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating; GDS = Geriatric Depression Scale; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - the Alzheimer's Disease and Related Disorders Association; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders-Fourth edition; MCI = mild cognitive impairment; WMS-R = Wechsler Memory Scale-Revised edition; FAQ = Functional Activity Questionnaire; TIA = transitory ischemic attack.

[a]The SNAC-K is a population-based study that recruited healthy elderly people without dementia living in the area of Kungsholmen/Essingeöarna (Stockholm). Some participants turned out to have MMSE scores below 24. For the purposes of this study, selection criteria based on previous SNAC-K studies (Ferencz et al., 2013; Qiu et al., 2012; Wang et al., 2014) were applied.

[b]The SNAC-K is a population-based study that recruited healthy elderly people without dementia living in the area of Kungsholmen/Essingeöarna (Stockholm). Some participants turned out to have medical conditions associated with cognitive impairment. For the purposes of this study, selection criteria based on previous SNAC-K studies (Ferencz et al., 2013) were applied. In particular, the following participants were excluded because of psychiatric disorder ($n = 27$), neurological disease ($n = 11$), MMSE < 24 ($n = 2$), and alcohol dependence syndrome ($n = 3$). Moreover, 49 further participants were excluded due to suboptimal MRI image quality.

TABLE 3 Demographic variables, clinical variables, and hippocampal volume

	AddNeuroMed	ADNI	AIBL	BRC	GENIC	BioFINDER	PIVUS	SNAC-K	*p*	η^2_{par}
Sample size, *n*	100	226	155	59	295	279	398	446	–	–
Age, mean (SD)	74.2 (5.6)	76.0 (5.1)	72.8 (7.1)	77.2 (5.8)	54.2 (10.7)	73.2 (5.1)	75.0 (0.0)	70.2 (8.9)	<.001	0.52
Age, range	61–88	60–90	60–88	67–91	35–83	65–87	75	60–96	–	–
Gender, % female	57%	48%	52%	59%	54%	61%	47%	40%	.002	0.01
Education, years	10.1 (4.5)	16.1 (2.8)	–	13.0 (3.4)	–	11.9 (3.7)	–	12.5 (4.5)	<.001	0.17
Education, % high level[a]	52%	98%	93%	88%	58%	72%	43%	73%	<.001	0.15
MMSE, mean (SD)	29.0 (1.3)	29.1 (1.0)	28.7 (1.2)	29.1 (1.1)	28.8 (1.3)	29.0 (0.9)	28.7 (1.4)	29.1 (1.0)	<.001	0.03
MMSE, range	25–30	25–30	25–30	26–30	24–30	27–30	21–30	25–30	–	–
Memory complaints, %	25%	–	56%	44%	27%	0%	–	72%	<.001	0.32
CDR, score (%)	0 (98%). 0.5 (2%)	0 (100%)	0 (94%). 0.5 (6%)	0 (100%)	–	0 (100%)	–	0 (0%)	<.001	0.04
Activities of daily living	-	**FAQ:** 0.1 (0.6)	–	–	**FAQ**: 0.4 (0.8)[c]	–	–	–	<.001	0.03
	–	–	–	–	–	–	–	**KATZ**: 0.0 (0.0)	–	–
Depressive symptomatology	**GDS:** 5.5 (1.1)	**GDS:** 0.9 (1.2)	**GDS:** 1.0 (1.3)	**GDS:** 1.7 (2.1)	**GDS:** 2.4 (2.2)[d]	-	–	-	<.001	0.43
	–	–	**HADS:** 2.6 (2.2)	–	–	**HADS:** 2.0 (2.3)	–	-	.008	0.02
	–	–	–	–	–	**CSDD**: 1.0 (2.3)	–	-	–	–
	–	–	–	–	–	–	–	**MADRS**: 1.8 (2.6)		
Mild depression,%[b]	40%	0%	4%[e]	7%	10%	3%[e]	–	1%	<.001	0.17
APOE ϵ4, % carriers	33%	27%	42%	33%	–	29%	–	26%	.010	0.01
TIV, dm^3	1.48 (0.14)	1.53 (0.17)	1.53 (0.16)	1.46 (0.19)	1.46 (0.16)	1.56 (0.16)	1.55 (0.16)	1.52 (0.25)	<.001	0.03
Global brain atrophy	23.5 (11.1)	24.7 (11.5)	28.2 (12.8)	25.0 (10.6)	47.3 (19.2)	24.5 (10.7)	21.2 (8.5)	31.6 (14.1)	<.001	0.30
Hippocampal volume, mm^3	7013 (865)	7118 (888)	7492 (890)	6803 (903)	8244 (1036)	7133 (945)	6929 (764)	7504 (968)	<.001	0.19

ADNI = Alzheimer's Disease Neuroimaging Initiative; AIBL = Australian Imaging Biomarkers and Lifestyle study; BRC = King's Health Partners Biomedical Research Centre for Mental Health Dementia Cohort; GENIC = Group of Neuropsychological Studies from the Canary Islands; PIVUS = Prospective Investigation of the Vasculature in Uppsala Seniors; SNAC-K = Swedish National Study on Aging and Care in Kungsholmen; SD = standard deviation; MMSE = mini-mental state examination; CDR = clinical dementia rating; ADL = activities of daily living; FAQ = functional activities questionnaire; KATZ = Katz Index of independence in activities of daily living; GDS = geriatric depression scale; HADS = hospital anxiety and depression scale; CSDD = Cornell scale for depression in dementia; MADRS = Montgomery-Asberg depression rating scale; APOE ϵ4 = apolipoprotein E allele ϵ4; TIV = total intracranial volume; dm^3 = cubic decimeters; mm^3 = cubic millimeters. The BV/CSF index was studied as a proxy of global brain atrophy. Hippocampal volume was calculated by summing left and right sides. Bonferroni correction for multiple comparisons (p value $\leq$ .003).

[a]Years of education was dichotomized in high and low level to allow comparability between cohorts providing years of education and those only providing levels of education. High level of education corresponds with 9 or more years of education, while low level of education corresponds with <9 years of education.

[b]Clinical cut-offs used for determining mild depression are the ones originally proposed in the scales: GDS $\geq$ 6 (Wancata, Alexandrowicz, Marquart, Weiss, & Friedrich, 2006); HADS $\geq$ 8 (Zigmond & Snaith, 1983); and MADRS $\geq$ 13 (Magnil, Janmarker, Gunnarsson, & Björkelund, 2013; Svanborg and Ekselius, 2003).

[c]FAQ in GENIC (11 items) was converted to the same scale than FAQ in ADNI (10 items) (conversion factor = 0.909).

[d]GDS values for 158 individuals were estimated from BDI by applying the following formula: BDI_to_GDS = (BDI z score × SD of GDS) + mean of GDS. SD and mean of GDS were calculated from the same population (N = 134).

[e]Percentage obtained from the HADS scale.

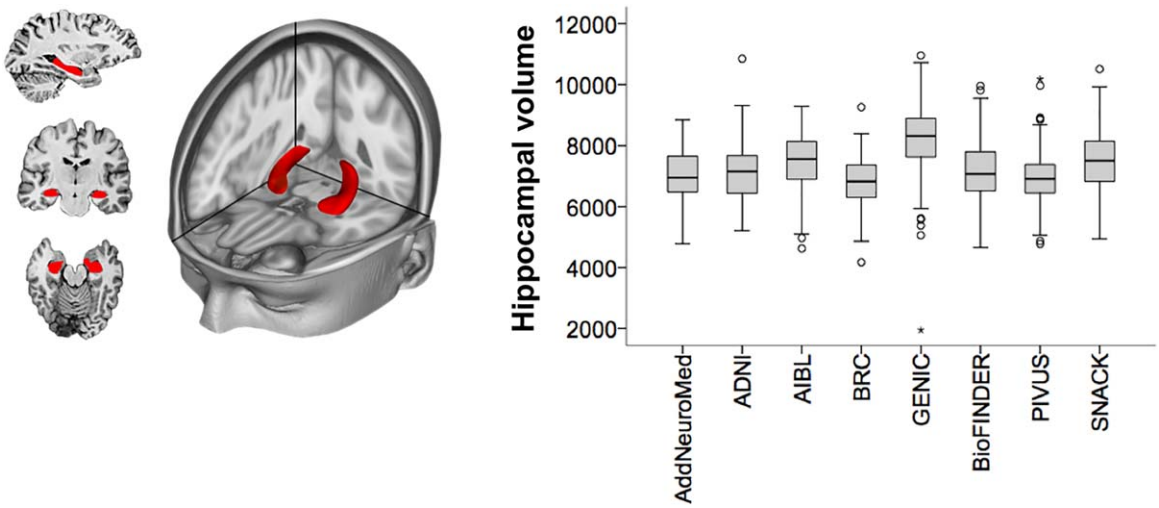

FIGURE 1 Between-cohort differences in hippocampal volume. Hippocampal volume was calculated by summing left and right sides and values are expressed in cubic millimeters. Values represent median and confidence intervals. ADNI = Alzheimer's Disease Neuroimaging Initiative; AIBL = Australian Imaging Biomarkers and Lifestyle study; BRC = King's Health Partners Biomedical Research Centre for Mental Health Dementia Cohort; GENIC = Group of Neuropsychological Studies from the Canary Islands; PIVUS = Prospective Investigation of the Vasculature in Uppsala Seniors; SNAC-K = Swedish National Study on Aging and Care in Kungsholmen [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Effect of demographic and clinical variables on hippocampal volume (whole sample)

(a) Importance Multiple regression model: $R^2 = 53\%$; $F_{(6,\ 1905)} = 355.747$; $p < .001$				(b) Interactions Multiple regression model: $R^2 = 57\%$; $F_{(14,\ 1897)} = 180.710$; $p < .001$			
Predictors (X)	***B***	***p***	***i***	**Predictors (X)**	**Unstandardized beta**	***T* value**	***p***
Age	−0.363	<.001	22%	Age	−42.083	−20.135	<.001
BV/CSF index	0.384	<.001	18%	BV/CSF index	32.785	21.597	<.001
TIV	0.369	<.001	9%	TIV	0.002	20.417	<.001
Gender	0.056	.004	3%	Gender	99.756	2.663	.008
Education level	0.058	<.001	1%	Education level	71.363	2.090	.037
MMSE	0.055	<.001	1%	MMSE	34.486	2.543	.011
				BV/CSF index × Age	0.975	11.307	<.001
				BV/CSF index × Gender	9.189	4.329	<.001
				BV/CSF index × Education level	−6.735	−2.246	.025
				Age × MMSE	3.802	2.921	.004
				Age × Education level	−13.147	−2.967	.003
				Gender × Education level	192.786	2.398	.017
				Gender × TIV	0.001	2.056	.040
				Education level × TIV	−0.001	−2.715	.007

i = importance from dominance analysis in multiple linear regression. It reflects the relative percentage of the variance of the regression model explained by a given predictor; TIV = total intracranial volume; MMSE = Mini-Mental State Examination; Gender (0 female; 1 male); Education Level (0 low; 1 high). High level of education corresponds with 9 or more years of education, while low level of education corresponds with <9 years of education. All possible interactions among age, the BV/CSF index, TIV, gender, education level, and MMSE were tested. Only significant ($p < .05$) predictors and interactions are presented in the table. Predictors included in the models can be consulted at Supporting Information Table 4. The BV/CSF index was studied as a proxy of global brain atrophy.

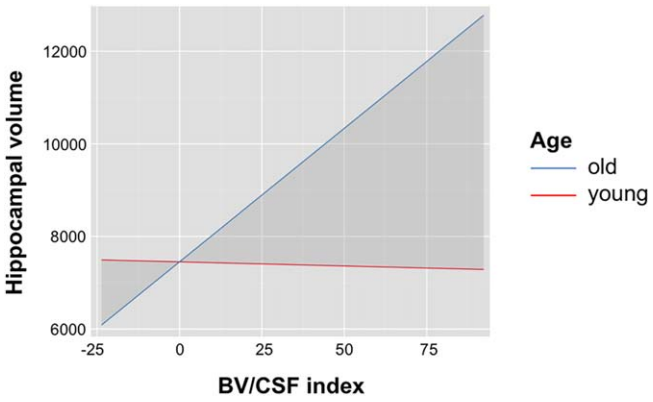

FIGURE 2 Effect of demographic and clinical variables on hippocampal volume (whole sample): significant interaction between age and the BV/CSF index (multiple linear regression: interaction between the effects of global brain atrophy (i.e., BV/CSF index) and age on hippocampal volume: unstandardized beta = 0.975; $t_{(1897)} = 11.307$; two-sided $p < .001$. $N = 1912$). Hippocampal volume was calculated by summing left and right sides. The BV/CSF index was studied as a proxy of global brain atrophy. Two groups were created by separating the upper bound of age (old) versus the lower bound of age (young). *y*-axis represents raw hippocampal volume in mm^3 and *x*-axis represents mean centered values of the BV/CSF index [Color figure can be viewed at wileyonlinelibrary.com]

3.3 | Effect of demographic and clinical variables on hippocampal volume

Multiple regression analyses performed for the whole sample showed that age and the BV/CSF index were the most important variables in explaining variability in hippocampal volume (Table 4a). Age and the BV/CSF index correlated with each other ($r = -.575$; $p < .001$). Moreover, both variables were not only important themselves but also in interaction with gender, education, MMSE, and TIV (Table 4b). Figure 2 shows the interaction between age and the BV/CSF index (unstandardized beta = 0.975; $t_{(1897)} = 11.307$; $p < .001$): smaller hippocampal volume was associated with lower BV/CSF index (i.e., more atrophy) in the older participants, but not in the younger ones. We then repeated the same multiple regression model for each separate cohort, also including depressive symptoms as a predictor. The association between hippocampal volume and the different demographic and clinical variables was modulated by the cohort factor (Figure 3). Patterns of association were largely the same across cohorts. Age, the BV/CSF index, and TIV showed the largest standardized regression coefficients (absolute $\beta > 0.20$), although education, MMSE, and depressive symptoms also showed significant associations especially in the population-based cohorts (absolute $\beta = 0.08$–0.12). Finally, we performed new multiple regression models for each separate cohort, but this time including all the available demographic and clinical variables (predictors included on each model are specified in Supporting Information Table 2 "Extended model"). Results indicated similar patterns as above but three new variables showed significant association with hippocampal volume. Higher scores in the CDR, presence of the APOE ϵ4 allele, and higher levels of CSF *T*-tau were significantly associated with smaller hippocampal volume ($\beta = -0.15$; $\beta = -0.17$; $\beta = -0.18$, respectively).

3.4 | Between-cohort differences in hippocampal volume are largely explained by between-cohort differences in demographic and clinical variables

An ANCOVA was performed to test between-cohort differences in hippocampal volume when accounting for the effect of age, gender, education, MMSE, TIV, and the BV/CSF index. Results showed a

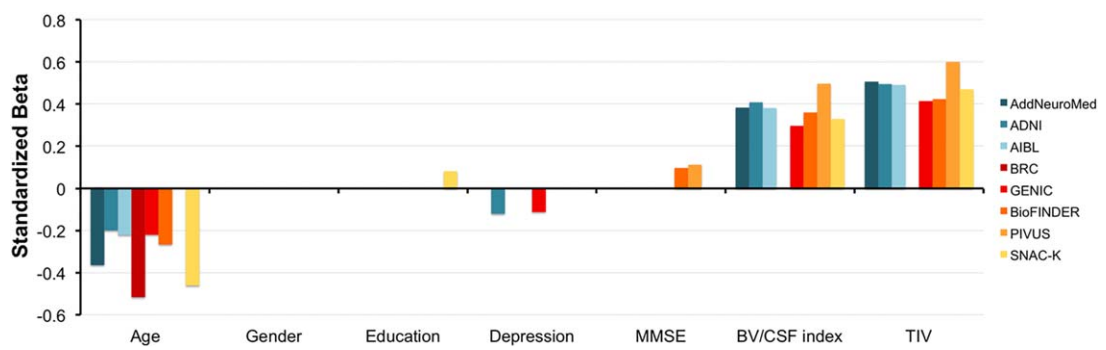

FIGURE 3 Effect of demographic and clinical variables on hippocampal volume (separately by cohorts). The figure schematizes the results from the multiple regression models (backwards) performed separately for the eight study cohorts. Only predictors remaining in the final models are displayed (criterion for excluding predictors from the models: two-sided $p < .10$). Predictors included in the original models as well as sample size can be consulted in Supporting Information Table 2. *p* Values of the primary regression models were adjusted using Bonferroni correction for multiple comparisons. Gender (0 female; 1 male); education level (0 low; 1 high). High level of education corresponds with 9 or more years of education, while low level of education corresponds with <9 years of education. Depression was measured with GDS (AddNeuroMed, ADNI, AIBL, BRC, and GENIC), HADS (BioFINDER), and MADRS (SNAC-K). The BV/CSF index was studied as a proxy of global brain atrophy. ADNI = Alzheimer's Disease Neuroimaging Initiative; AIBL = Australian Imaging Biomarkers and Lifestyle study; BRC = King's Health Partners Biomedical Research Centre for Mental Health Dementia Cohort; GENIC = Group of Neuropsychological Studies from the Canary Islands; PIVUS = Prospective Investigation of the Vasculature in Uppsala Seniors; SNAC-K = Swedish National Study on Aging and Care in Kungsholmen; MMSE = mini-mental state examination; TIV = total intracranial volume [Color figure can be viewed at wileyonlinelibrary.com]

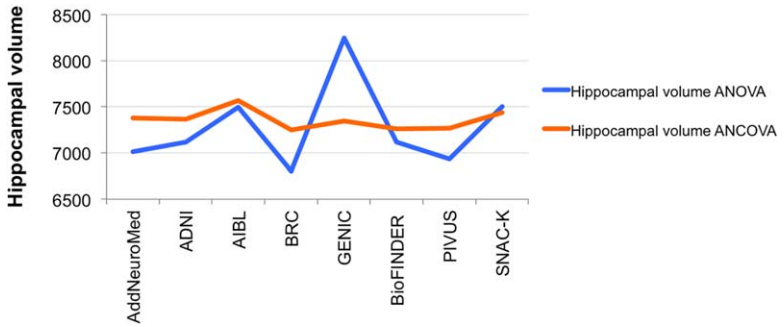

FIGURE 4 Attenuation of between-cohort differences in hippocampal volume when controlling for demographic and clinical variables (ANOVA: $F_{(7,\ 1904)} = 63.188$; two-sided $p < .001$; $\eta^2_{par} = 19\%$; ANCOVA: $F_{(7,\ 1898)} = 4.429$; two-sided $p < .001$; $\eta^2_{par} = 2\%$). The original ANOVA ($N = 1958$) was repeated for the same sample size than the ANCOVA ($N = 1912$) to allow perfect comparability of the results. Hippocampal volume was calculated by summing left and right sides and values are expressed in cubic millimeters. Covariates included in the ANCOVA model are age, gender (0 female; 1 male), education level (0 low; 1 high), MMSE, TIV, and the BV/CSF index. High level of education corresponds with 9 or more years of education, while low level of education corresponds with <9 years of education. The BV/CSF index was studied as a proxy of global brain atrophy. ADNI = Alzheimer's Disease Neuroimaging Initiative; AIBL = Australian Imaging Biomarkers and Lifestyle study; BRC = King's Health Partners Biomedical Research Centre for Mental Health Dementia Cohort; GENIC = Group of Neuropsychological Studies from the Canary Islands; PIVUS = Prospective Investigation of the Vasculature in Uppsala Seniors; SNAC-K = Swedish National Study on Aging and Care in Kungsholmen; MMSE = mini-mental state examination; TIV = total intracranial volume [Color figure can be viewed at wileyonlinelibrary.com]

dramatic reduction in the effect size from 19% in the original ANOVA for between-cohort differences in hippocampal volume ($F_{(7,\ 1904)} = 63.188$; $p < .001$) (Table 3) to 2% in this ANCOVA ($F_{(7,\ 1898)} = 4.429$; $p < .001$). Moreover, most post hoc comparisons became non-significant. AIBL and SNAC-K displayed the largest hippocampal volumes, significantly different from those found in BioFINDER and PIVUS. The effect sizes of the covariates showed that TIV ($\eta^2_{par} = 15\%$), the BV/CSF index ($\eta^2_{par} = 13\%$), and age ($\eta^2_{par} = 9\%$), had the strongest confounding effect. Figure 4 shows how original between-cohort differences in hippocampal volume (blue line) are attenuated when controlling for the aforementioned covariates (orange line).

4 | DISCUSSION

In this study, age and global brain atrophy (i.e., BV/CSF index) were the most important variables in explaining variability in hippocampal volume, and were not only important themselves but also in interaction with gender, education, MMSE, and TIV. AddNeuroMed, ADNI, and AIBL differed from population-based cohorts in key demographic and clinical variables that were found to largely explain between-cohort differences in hippocampal volumes. Below we discuss several important implications of the findings as well as considerations for generalization of results from these highly selected samples to the general population.

Age was the most important variable in explaining differences between cohorts, followed by education level, TIV, and the BV/CSF index. Participants in ADNI and AddNeuroMed were older in comparison with AIBL and most of the population-based cohorts. This result is different from previous studies where the control groups from ADNI and AIBL were younger than those from the population-based cohorts of the Mayo Clinic Study of Aging (MCSA) and the Sydney Memory and Aging Study, respectively (Brodaty et al., 2014; Whitwell et al., 2012). Of note, because of the recent interest in studying the preclinical stage of AD (Sperling et al., 2011), as well as in conducting aging research from a lifespan perspective (Walhovd, Fjell, & Espeseth, 2014), especially focused on middle-age populations (Ferreira et al., 2015), there is a clear trend for contemporary aging studies to include younger cohorts than those of AddNeuroMed and ADNI.

As previously reported, education levels were found to be considerably higher in ADNI and AIBL compared to AddNeuroMed and most of the population-based cohorts (Brodaty et al., 2014; Whitwell et al., 2012). Education is one of the most frequently used proxies of cognitive reserve (Stern, 2009). Therefore, this finding has important implications as extensive evidence exist about the impact of cognitive reserve in both cognition and brain structure. It has previously been suggested that a large proportion of the ADNI controls could be on the path to AD dementia, although cognitive reserve mechanisms may have protected them from cognitive decline (Whitwell et al., 2012).

Regarding TIV, the cohorts of BRC and GENIC showed the smallest TIV values while ADNI, AIBL, BioFINDER, and PIVUS showed the largest. Whitwell et al. (2012) did not find significant differences in TIV between healthy individuals in ADNI and MCSA. Larger TIV has previously been related to higher brain reserve and protection against AD pathology (Stern, 2009; Whitwell, 2010). The fact that individuals in the ADNI cohort have larger TIV in combination with higher level of education is thus of interest. A recent study showed that larger TIV attenuated the impact of brain atrophy on clinical disease progression in the MCI patients from ADNI (Guo, Alexopoulos, Wagenpfeil, Kurz, & Perneczky, 2013).

The cohorts AIBL, GENIC, and SNAC-K had less brain atrophy (i.e., higher BV/CSF index) compared to AddNeuroMed and PIVUS. We are not aware of previous studies comparing the control groups from

AddNeuroMed, ADNI, or AIBL versus population-based cohorts in terms of global brain atrophy. When looking at other imaging markers, previous studies have reported higher rates of hippocampal atrophy (Whitwell et al., 2012), reduced cortical volume (Nettiksimmons et al., 2010), and unusually high amyloid load (Jagust et al., 2009) in the ADNI cohort. In AIBL, GENIC, and SNAC-K, less global brain atrophy (i.e., higher BV/CSF index) could be explained by the fact that these cohorts have the youngest participants. Low educational level, relatively old participants, and high prevalence of mild depression (40%) may explain why the subjects in AddNeuroMed and PIVUS had a lower BV/CSF index. Vascular comorbidity and vascular risk factors were also frequent in PIVUS (Lind, Fors, Hall, Marttala, & Stenborg, 2005). All these factors have previously been associated with brain atrophy (Janowitz et al., 2014; Jiang et al., 2014; Noble et al., 2012; Raz et al., 2010; Shpanskaya et al., 2014; Yuefeng et al., 2014).

We also found between-cohort differences in gender distribution, MMSE, CDR, presence of subjective memory complaints, depressive symptomatology, and APOE ϵ4 distribution. The effect of these and the previously discussed factors of age, education, TIV, and global brain atrophy on hippocampal volume is widely known. However, limited research has focused on cognitively normal individuals (Crivello et al., 2010; Janowitz et al., 2014; Jiang et al., 2014; Morra et al., 2009; Noble et al., 2012; Raz et al., 2010; Shpanskaya et al., 2014; Striepens et al., 2011; Voevodskaya et al., 2014; Yamaguchi et al., 2002; Yuefeng et al., 2014), and negative results have also been reported (Janowitz et al., 2014; Jiang et al., 2014; Morra et al., 2009; Shpanskaya et al., 2014; Striepens et al., 2011; Yamaguchi et al., 2002; Yuefeng et al., 2014). An explanation for these conflicting results is that all previous studies have focused on one or a few of the factors at a time. Therefore, some of the missing factors could be exerting an unobserved confounding effect and partially drive the results.

Increasing evidence shows that some of these factors play a relevant role in disease progression [e.g., cognitive reserve (Sperling et al., 2011)], magnifying variability on rates of hippocampal decline along the stages of MCI and AD. Therefore, the influence of several key demographic and clinical factors on brain structure and disease progression may add something valuable to the explanation of different subtypes in AD.

The main contribution of this study is the demonstration that once all these factors are simultaneously considered, age and global brain atrophy are the most important factors in explaining variability in hippocampal volume. These variables were not only important in themselves but also in interaction with gender, education, MMSE, and TIV. The fact that global brain atrophy (i.e., the BV/CSF index) strongly correlated with age indicates that reduced hippocampal volume in cognitively normal individuals seems to be primarily explained by a process of global brain atrophy, presumably age related. This would be true only for the older individuals. The interaction obtained suggests that reduced hippocampal volume in younger individuals could be indicative of either preclinical pathological changes related to a certain neurodegenerative disease or simply premorbid small hippocampal volume.

A previous study also found differences between ADNI controls and a population-based cohort in key demographic and clinical variables (Whitwell et al., 2012). In that study, hippocampal volume was larger in the ADNI controls than in those from the MCSA cohort and these differences were no longer significant after matching the cohorts by age, gender, education, APOE ϵ4 genotype, and MMSE. To the best of our knowledge, the control groups from AIBL and AddNeuroMed have not been previously compared with population-based cohorts in terms of hippocampal volume. Our results together with recent research (Brodaty et al., 2014; Whitwell et al., 2012) demonstrate that control groups from ADNI, AIBL, and AddNeuroMed may not be representative of the general population.

This study has several strengths: (a) the use of the largest sample to date in a study of this kind ($N = 1{,}958$); (b) the inclusion and comparison of the three currently most widely used multicenter cohorts in dementia imaging research (i.e., AddNeuroMed, ADNI, and AIBL); and (c) the interactive evaluation of several demographic and clinical variables associated with hippocampal volume, in contrast to virtually all previous studies frequently investigating these factors in a separate manner.

Some limitations should also be considered. Some variables were missing for some of the cohorts, limiting the consideration of several clinical variables when performing analyses at the whole-sample level. This was addressed by running analyses for each separate cohort including all the available variables. Furthermore, imaging data from different centers with different MRI equipment and sequences were used. This affects only those analyses where the different cohorts were combined or compared to each other, but not those analyses carried out for the separate samples. Moreover, most of the MRI sequences were designed to be comparable with the ADNI protocol. Some factors could still have some influence in the imaging measurements, especially differences in field strength. Nonetheless, excellent agreement between hippocampal volumes measured across different field strengths has been previously demonstrated for FreeSurfer (Briellmann, Syngeniotis, & Jackson, 2001; Whitwell et al., 2012). Other studies have also compared cohorts where MRI data were acquired in different centers, equipment, and field strengths (Hibar et al., 2015; Whitwell et al., 2012). Still, we cannot know how much of the variance in hippocampal volume is due to scanners and protocol differences in this study. Finally, several life-style factors such as smoking and cardiometabolic factors have been previously identified as determinants of hippocampal volume in cognitively normal individuals (Janowitz et al., 2014) but were not considered in this study.

5 | CONCLUSION

This study may have important implications for the use of hippocampal atrophy as a biomarker. The results highlight the large variability in hippocampal volume during the cognitively normal stage. This is important when trying to disentangle disease mechanisms from the effect of several demographic and clinical factors. Another important conclusion is that the samples of AddNeuroMed, ADNI, and AIBL are not representative of the general population. Both conclusions must be taken into account when (a) designing research where a clinical group is recruited

from a specialized center and compared with a control group from the general population; (b) designing future clinical trials, which are often based on highly selected populations; (c) translating imaging biomarkers to the general population; and (d) applying the new diagnostic criteria for AD and predementia stages, in which imaging biomarkers are important for increasing certainty about the underlying disease (Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011). The key factor here is how well knowledge can be translated from clinical settings to the general population, and vice versa. The strategy for recruiting individuals will depend on the study aims and the materials to be used. Regarding hippocampal atrophy as a biomarker, our findings show that age and global brain atrophy are the most important factors to be considered, but gender, education, MMSE, and TIV should also be taken into account.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Supplementary Table 1 Methods for collection and analysis of CSF and MRI data

Supplementary Table 2 Description of statistical analyses

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