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Frequency of cognitive "super-aging" in three Australian samples using different diagnostic criteria

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ABSTRACT

Objectives: To investigate the frequency of exceptional cognition (cognitive super-aging) in Australian older adults using different published definitions, agreement between definitions, and the relationship of super-aging status with function, brain imaging markers, and incident dementia.

Design: Three longitudinal cohort studies.

Setting: Participants recruited from the electoral roll, Australian Twins Registry, and community advertisements.

Participants: Older adults (aged 65–106) without dementia from the Sydney Memory and Ageing Study ($n = 1037$; median age 78), Older Australian Twins Study ($n = 361$; median age 68), and Sydney Centenarian Study ($n = 217$; median age 97).

Measurements: Frequency of super-aging was assessed using nine super-aging definitions based on performance on neuropsychological testing. Levels of agreement between definitions were calculated, and associations between super-aging status for each definition and functioning (Bayer ADL score), structural brain imaging measures, and incident dementia were explored.

Results: Frequency of super-aging varied between 2.9 and 43.4 percent with more stringent definitions associated with lower frequency. Agreement between different criteria varied from poor (K = 0.04, AC1 = .24) to very good (K = 0.83, AC1 = .91) with better agreement between definitions using similar tests and cutoffs. Super-aging was associated with better functional performance (4.7–11%) and lower rates of incident dementia (hazard ratios 0.08–0.48) for most definitions. Super-aging status was associated with a lower burden of white matter hyperintensities (3.8–33.2%) for all definitions.

Conclusions: The frequency of super-aging is strongly affected by the demographic and neuropsychological testing parameters used. Greater consistency in defining super-aging would enable better characterization of this exceptional minority.

Keywords: super-ageing, super-agers, cognition, definition, imaging

Introduction

Cognition usually declines with age although there is considerable variability in the type and rate of deterioration between individuals. Domains particularly vulnerable to aging include processing speed, working and episodic memory, and verbal and conceptual reasoning (Blazer, 2006; Cadar, 2018). Cognitive "super-aging," referred to henceforth as super-aging, has been used to describe a subset of older individuals who demonstrate superior cognitive abilities based upon specific criteria (Gardener *et al.*, 2021; Harrison *et al.*, 2012). Definitions of super-aging and related terms such as "high-performing older adults," "supernormals" and "cognitively elite" vary between studies, and it is therefore difficult to establish its prevalence or make large-scale associations between super-aging status and health outcomes.

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Several definitions of super-aging have been proposed. Some features are consistent across definitions including the selection of older adults and the requirement that these individuals be outliers for their age group regarding cognition with an emphasis on episodic memory performance. However, super-aging samples have ranged in age from those in their late 60s (Bott *et al.*, 2017; Cabeza *et al.*, 2002; Dang *et al.*, 2019; Saint Martin *et al.*, 2017; Yu *et al.*, 2020) to 80 years and above (Harrison *et al.*, 2012; Rogalski *et al.*, 2013) as have comparator groups. Some researchers have selected people with superior cognition compared to same-age peers; others have required cognitive performance equivalent to younger adults ranging in age from 18 (Sun *et al.*, 2016; de Godoy *et al.*, 2021) to 65 years (Harrison *et al.*, 2012; Bezdicek *et al.*, 2021). Maintenance of superior cognitive performance over time has been incorporated into several definitions (Baran and Lin, 2018; Bott *et al.*, 2017; Dekhtyar *et al.*, 2017; Gardener *et al.*, 2021; Lin *et al.*, 2017; Maccora, *et al.*, 2020; Bezdicek et al., 2021). The cognitive tests and performance cutoffs used have also differed between studies with assessment of verbal episodic memory using a word list learning task most commonly included, with or without superior performance required in other domains including attention, processing speed, and executive function (Borelli *et al.*, 2018). Superior cognitive processing speed is the only other single domain that has been used in a super-aging definition (Bott *et al.*, 2017). No previous study has compared the performance of these definitions within the same population.

A uniform approach to the identification of super-agers could lead to a better understanding of predictors of high cognitive performance and identify potential interventions to help maintain cognitive capacities into advanced age. Genetic, lifestyle, and neuropathological differences have been reported in the super-aging literature. Genetic differences in super-agers include lower rates of the apolipoprotein ε4 allele (*APOE4*) which is associated with an increased risk of Alzheimer's disease (Rogalski *et al.*, 2013) and variants in the mitogen-activated protein kinase 3 (*MAP2K3*) gene (Huentelman *et al.*, 2018). *MAP2K3* activity has been implicated in Alzheimer's disease via an inflammatory cascade, and variants observed in super-agers are associated with reduced activity and hence reduced inflammation (Huentelman *et al.*, 2018). Super-agers are less likely to be smokers or have diabetes and more likely to exhibit higher levels of intellectual and social activity than their cognitively average counterparts (Maccora, *et al.*, 2020; Saint Martin *et al.*, 2017). Both higher baseline cognitive function and stability of cognitive performance over time have been associated with greater social engagement in later life (Saint Martin *et al.*, 2017). Imaging studies of the brains of super-agers have demonstrated less cortical atrophy and greater structural integrity compared to control participants (Harrison *et al.*, 2012; Kim *et al.*, 2020; Sun *et al.*, 2016). Neuropathological studies have reported less but still significant Alzheimer's type pathology (Rogalski *et al.*, 2013, 2019). This suggests that both resistance and resilience to neurodegenerative pathology may underlie exceptional cognition in older age.

The first aim of this study was to compare the frequency of exceptional cognition or "super-aging" in cohorts of Australian older adults derived from three longitudinal studies based on existing published definitions. Secondly, we aimed to establish the extent to which existing definitions reliably identify the same individuals. Thirdly, we aimed to examine the association between super-aging status and three outcomes: i) functional status in terms of personal and instrumental activities of daily living, ii) structural brain imaging markers, and iii) incident dementia.

Materials and methods

Participants

Participants were drawn from three longitudinal studies: the Sydney Memory and Ageing Study (MAS), Older Australian Twins Study (OATS), and Sydney Centenarian Study (SCS). MAS commenced in 2005 with participants aged 70–90 years, living in the community and recruited from the electoral roll (Sachdev *et al.*, 2010). All participants were required to have sufficient English language proficiency to complete neuropsychological assessments. Exclusion criteria included major neurologic conditions (i.e. dementia, motor neuron disease, multiple sclerosis), psychiatric illness (i.e. schizophrenia, bipolar disorder), developmental disability, a Mini-Mental State Examination (MMSE) (Folstein, *et al.*, 1975) score ≤ 23 at study entry, or a diagnosis of dementia after initial comprehensive assessment. Additionally, active cancer or any other medical or psychological conditions that might hinder their ability to complete assessments were excluded (Sachdev *et al.*, 2010). Participants in OATS, which commenced in 2007, were recruited through the Australian Twin Registry and through advertisements, media campaigns, and clubs and networks of older citizens in the Eastern states of Australia including New South Wales, Victoria, and

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Queensland (Sachdev *et al.*, 2009). All participants were 65 years or older and had very similar inclusion and exclusion criteria to MAS, except for a diagnosis of dementia if participants were able to consent (Sachdev *et al.*, 2009). The SCS commenced in 2007 with participants aged 95 years and older recruited from the community and residential aged care facilities (RACFs) utilizing the electoral roll, media campaigns, local clinics, and outpatient services, directors of RACFs, older citizens' organizations, and other longitudinal studies (Sachdev *et al.*, 2013). Only those acutely or terminally ill were excluded (Sachdev *et al.*, 2013). Fourteen participants in OATS and 126 participants in SCS with dementia based on consensus clinical diagnoses at baseline were excluded from this study. We randomly selected only one of the OATS twin pairs and excluded siblings for this study. This resulted in a final sample size of 1615 participants (MAS $n = 1037$; OATS $n = 361$; SCS $n = 217$).

Neuropsychological measures

Participants in MAS underwent assessment of premorbid intelligence (National Adult Reading Test: (NART) (Nelson and Willison, 1991)), attention and processing speed (Digit Symbol Coding (Wechsler, 1997b) and Trail Making Test A:TMT-A (Reitan and Wolfson, 1993)), executive function (Trail Making Test B: TMT-B (Reitan and Wolfson, 1993)), memory (Logical Memory Story A (Wechsler, 1997a), Rey Auditory Verbal Learning Test: RAVLT (Rey, 1964) and Benton Visual Retention Test (Benton, *et al.*, 1966)), language and verbal fluency (Boston Naming Test – 30 items: BNT-30 (Kaplan, *et al.*, 2001), Controlled Oral Word Association Test: COWAT (Benton, 1967) and Semantic Fluency – Animals (Spreen and Benton, 1969)) and visuospatial function (Block Design: BD (Wechsler, 1981)) as well as cognitive screening with the MMSE (Sachdev *et al.*, 2010). The same assessments were conducted in OATS with the addition of Digit Span Forward and Backward (Wechsler, 1981), Mental Control (Wechsler, 1981), Similarities (Wechsler, 1997b), and the Stroop Color and Word Test 1, 2, and 3 (Delis *et al.*, 2004; Sachdev *et al.*, 2009). Neuropsychological testing was conducted for up to four waves of follow-up, approximately two years apart, for MAS and OATS (Sachdev *et al.*, 2009, 2010). Participants in SCS underwent a more limited battery of tests, including the NART (Nelson and Willison, 1991), Addenbrooke's Cognitive Examination-Revised (ACE-R)(Mathuranath *et al.*, 2000), Mental Control (Wechsler, 1997a), Similarities (Wechsler, 1997b), oral TMT-A and B (Ricker and Axelrod, 1994), COWAT (Benton, 1967), Hopkins Verbal Learning Test (HVLT) (Brandt, 1991), and the 15 item version of the BNT (BNT-15) (Kaplan, *et al.*, 2001; Sachdev *et al.*, 2013). A full neuropsychological testing battery was administered only once, at baseline, for SCS participants but the ACE-R was included in four waves of follow-up at least six months apart (Sachdev *et al.*, 2013).

Dementia diagnosis

MAS and OATS study participants who scored at least 1.5 standard deviations below published normative data in at least one cognitive domain or exhibited low neuropsychological testing scores and a decline in activities of daily living based on informant interview were brought to a case conference to determine a diagnosis. Consensus diagnosis was made by an expert team, including neuropsychiatrists, psychogeriatricians and neuropsychologists, on the basis of available clinical, neuropsychological, laboratory, and imaging data and using DSM-IV criteria (Sachdev *et al.*, 2009, 2010). For SCS participants, a panel of investigators examined scores on the MMSE, functional impairment questionnaires, and other available information to classify participants based on DSM-IV criteria (Sachdev *et al.*, 2013).

Brain imaging

All participants across the three studies were invited to undergo a brain magnetic resonance imaging (MRI) scan. MAS and SCS participants were scanned using a 3T Philips MRI scanner at the Prince of Wales Hospital in Randwick New South Wales with standard protocol including scout midsagittal cut for AC-PC plane alignment, 3D T1-weighted structural MRI acquired coronally, T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence and diffusion-weighted imaging(Sachdev *et al.*, 2010, 2013). OATS MRI data were collected from three centers using a 1.5T Siemens scanner in Melbourne and Brisbane and initially a 1.5 T Phillips scanner in Sydney which was later upgraded to a 3T scanner (Koncz *et al.*, 2018). Acquisition protocols were consistent across centers. Automated segmentation of the scans allowed for calculation of whole brain volumes (defined as the sum of gray matter and white matter volumes) and cortical volumes and a standard tracing protocol was used to obtain hippocampal volumes and anterior cingulate volumes. White matter hyperintensity volumes were obtained from the FLAIR images using a segmentation procedure with in-house developed software (Sachdev *et al.*, 2013). Volumetric data were available for 534 MAS participants, 192 OATS participants, and 25 SCS participants. Measurements were harmonized using the ComBat technique to account for

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unwanted sources of variation through the use of different scanners (Fortin *et al.*, 2018).

Super-aging classifications and determination of cognitive profiles

A literature review was performed through searches of PubMed (including MEDLINE), Embase, Web of Science, Scopus, PsycINFO, and Google Scholar using a comprehensive list of terms related to the broad concept of successful or super-aging and exceptional cognition from inception to 9th December 2021. The search was updated in December 2022. This identified 36 published studies of super-agers. The resulting 20 definitions could be grouped into three broad categories: i) cognitive performance comparable to younger adults, ii) cognitive performance superior for age, and/or iii) maintenance of superior cognitive abilities (i.e. lack of normative age-related decline). The cognitive domains, tests, and cutoffs selected differed between studies. Study objectives and contexts were also diverse. The components of the definitions referred to in this study are summarized in Table 1. More detailed components of all published super-aging definitions are presented in Supplementary Table 1. Data were available from the three longitudinal Australian cohorts to apply nine of these definitions. Super-agers were compared to non-super-agers in all three cohorts with non-super-agers defined as healthy participants without significant cognitive impairment but not meeting each of the super-aging criteria.

Statistical analyses

The following statistical analyses were performed using IBM™ SPSS™ 28 (IBM Corp, 2021) and the R package irrCAC (Gwet, 2019; R Core Team, 2023).

1. Assessment of frequency of super-aging based on different published definitions and agreement between definitions

Raw test scores from wave 1 of the three studies and/or other waves if the definition in question included longitudinal assessment were used to identify super-agers. Unweighted kappa statistics (κ) were calculated to measure the agreement rate between each set of super-aging criteria. As initial analyses indicated that kappa values were generally low, potentially due to a low frequency of super-agers rather than a low level of agreement (Feinstein and Cicchetti, 1990), Gwet's first-order agreement coefficient (AC1) was also calculated (Gwet, 2010). Kappa values were interpreted as follows: 0–0.20 (poor), 0.21–0.40 (fair), 0.41–0.60 (moderate), 0.61–0.80 (good), and 0.81–1.00 (very good) (Altman, 1991). AC1 is interpreted similarly to kappa (Gwet, 2010). Kappa values (κ) and 95% confidence intervals (CI) were reported.

2. Association of super-aging status with activities of daily living

Assessment of any difference in baseline instrumental activities of daily living (IADL; total score on the Bayer Activities of Daily Living Scale (Erzigkeit *et al.*, 2001)) between super-agers and non-super-agers was examined for each published definition. As the IADL scores did not meet the normality assumption and were positively skewed, generalized linear modeling (GLM) with a gamma distribution and a log-link function was used. Because of the use of a log-link function, the regression coefficients (b) were exponentiated (Exp(b)) and then used to represent percentage differences in IADL scores between the super-aging and non-super-aging groups. For Exp(b) smaller than 1, the super-aging group would have $(1 - \text{Exp}(b)) \times 100\%$ lower IADL scores than the non-super-aging groups. For Exp(b) larger than 1, the percentage change was calculated as $(\text{Exp}(b) - 1) \times 100\%$. The analysis controlled for physical health using proxies of ability to complete the sit-to-stand test (Bohannon, 1995), number of prescribed medications (Bertoldi, *et al.*, 2006; Fernandes *et al.*, 2019), and sensory impairment (hearing and vision) as well as age, sex, and study.

3. Association of super-aging status with structural brain imaging measures and burden of white matter disease

Whole brain volume, cortical volume, hippocampal volume, caudal anterior cingulate volume, and volume of white matter hyperintensities were selected as markers of brain aging (Cole *et al.*, 2019) and for consistency with previous super-aging studies (Katsumi *et al.*, 2022). These data were mostly normally distributed so generalized linear models with normal distribution and identity link were used to explore the associations between super-aging status for each of the definitions, and the imaging measures. Volume of white matter hyperintensities was positively skewed so GLM with a gamma distribution, and a log-link function was used for this, and regression coefficients were exponentiated and interpreted in the same way as the IADL analyses. These analyses were also controlled for age, sex, study, and the other variables included in the functional status analyses.

4. Association of super-aging status with incident dementia

Consensus diagnoses of dementia over available waves of follow-up for the three studies were recorded. A Cox regression analysis was used to evaluate the association between super-aging status according to the nine different definitions and incident dementia during available waves of follow-up. All analyses contained participants' age, sex, and study as covariates.

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Table 1. Components of published super-aging definitions used in this study

TERM (STUDY)	SAMPLE (MEAN AGE)	COGNITIVE DOMAIN/S	TESTS (CURRENT STUDY HAS AVAILABLE DATA ✓/X)	CUTOFFS
Cognition comparable to younger adults in ≥ 1 domain				
Definition 1 'Super-agers'				
Gefen *et al*, 2014, Harrison *et al*. 2012, Rogalski *et al*. 2013, Gefen *et al*. 2014, Cook *et al*. 2017, Cook Maher *et al*. 2017, Huentelman *et al*. 2018, Janeczek *et al*. 2018, Rogalski *et al*. 2019, Cervenkova *et al*. 2020, Borelli *et al*. 2021, Karpouzian-Rogers *et al*. 2022, Nassif *et al*. 2022	≥ 80 (mean age 84.6)	Verbal episodic memory	RAVLT delayed recall (✓)	≥ 9/normative mean for 50–65yo
		Executive function, verbal fluency, language/naming	TMT-B (✓), CFT (✓), BNT-30 (✓)	At least average (≥ − 1 SD for age and education)
Definition 2 'Super-agers'				
Dang *et al*. 2019	68.4	Verbal episodic memory	CVLT delayed recall (x)[a]	≥ normative mean for 30–40yo
		Executive function, working memory, verbal fluency	Digit symbol substitution (✓), Stroop (x), digit span (✓), letter and category fluency (✓)	≥ − 1 SD mean for age
Definition 3 'Super-agers'				
Sun *et al*, 2016, Zhang *et al*. 2020, Katsumi *et al*. 2022	67.8	Verbal episodic memory	CVLT long delay-free recall (x)[a]	≥ gender-adjusted normative mean for 18–32yo
		Executive function	TMT-B (✓)	≥ − 1 SD mean for age
Definition 4 'Super-agers'				
Maccora *et al*, 2020	70.4 F, 70.2 M	Verbal episodic memory	CVLT immediate and delayed recall (x)[a]	*Maintaining* scores ≥ median for those of the same gender in their 20s
		Global cognition	MMSE (✓)	≥ 29 over three waves of follow-up
Definition 5 'Resilient agers'				
Bott *et al*, 2017	69.2	Cognitive processing speed	Computerized test (x)[b]	Scores within 1.25 SD of young adult comparator group in their 20s and *<0.5 SD decline at follow-up* (mean 2.5 years)

Table 1. Continued

TERM (STUDY)	SAMPLE (MEAN AGE)	COGNITIVE DOMAIN/S	TESTS (CURRENT STUDY HAS AVAILABLE DATA ✓/x)	CUTOFFS
Superior cognition for age in ≥ 1 domain				
Definition 6 'Supernormals'				
Lin *et al*, 2017	73.5	Episodic memory composite	MMSE (✓), ADAS-Cog (x), RAVLT (✓), logical memory (✓)	> 1.5 SD of sample *across available study visits* (≥ 1 follow-up)
Definition 7 'Successful cognitive aging'				
Mapstone *et al*. 2017	83.2	Verbal episodic memory	RAVLT learning, retrieval, and recognition composite (✓)	Scores ≥ 90th percentile of sample
		Global cognition, executive function, attention, verbal fluency, language/ naming, visuospatial	MMSE (✓), TMT-A and B (✓), CFT (✓), BNT-60, forward and backward digit span (✓), HVOT (x)	> − 1.35 or >10th percentile of all other domain composite scores
Definition 8 'Top Cognitive Performers'				
Dominguez *et al*, 2021	2 cohorts: 74.1, 94.1	Verbal episodic memory and executive function	Logical memory delayed (✓) and TMT-B (✓) for <90yo, CVLT delayed recall (x)[a] and TMT-B (✓) for >90yo	Within the top 50th percentile of the sample for younger group, within the top 50% expected for age for older group
Definition 9 'Super-cognition'				
Yu *et al*, 2020	67.3	RBANS: immediate memory, visuospatial, language, attention, delayed	Word list learning (✓)[a], story (✓), figure copy (x)[c], line orientation (x), picture naming (✓), category fluency (✓), digit symbol test (✓), list recall (✓), list recognition (✓), story (✓), figure recall (x)	Score ≥ 1 SD above age and education-appropriate norms in ≥ 1 domain and ≥ average performance in all other domains
		Function	CDR	0

Three definitions (4, 5, and 6) required maintenance of exceptional cognition.

ADAS-Cog: Alzheimer's Disease Assessment Scale – Cognitive Subscale, BNT-30: 30-item Boston Naming Test, BNT-60: 60-item Boston Naming Test, CDR: Clinical Dementia Rating scale, CFT: Category Fluency Test, CVLT: California Verbal Learning Test, HVLT: Hopkins Verbal Learning Test, HVOT: Hooper Visual Organization Test, MMSE: Mini-Mental State Examination, RAVLT: Rey Auditory Verbal Learning Test, RBANS: Repeatable Battery for the Assessment of Neuropsychological Status, SD: standard deviation, TMT-A and B: Trail Making Test Parts A and B.

[a]RAVLT substituted for this study, HVLT for SCS participants.

[b]TMT-A substituted.

[c]Block design substituted for visuospatial measures for MAS and OATS participants, visuospatial subdomain of ACE-R for SCS.

Table 2. Participant characteristics

	TOTAL SAMPLE ($N = 1615$)	MAS ($N = 1037$)	OATS ($N = 361$)	SCS ($N = 217$)
Demographics				
Female (%)	58%	572 (55.2)	220 (60.9)	144 (66.4)
Median age (IQR)	78 (10)	78 (8)	68 (7)	97 (2)
Education – years, median (IQR)	11 (5)	11 (5)	11 (5)	9 (3)
Daily functioning				
Median total iADL score (IQR)	1.3 (0.8)	1.3 (0.6)	1.2 (0.6)	3.4 (5.9)
Other				
Number of medications, median (IQR)		4 (4)	3 (5)	5 (5)
Sit to stand (s), median (IQR)		16 (7)	13 (5)	86:107[a]
Hearing impairment (%)		423/1036 (40.8)	73/301 (24.3)	138/176 (72)
Visual impairment (%)		100/1032 (9.7)	26/308 (8.4)	91/131 (69.5)[b]
History of stroke (%)		41/1026 (4.0)	8/308 (2.6)	11/210 (5.2)
Head injury[c] (%)		156/1035 (15.1)	48/309 (15.5)	42/208 (20.2)
Depression ever[d] (%)		163/1002 (16.3)	59/306 (19.3)	8/217 (3.7)
Diabetes mellitus (%)		126/1032 (12.2)	24/309 (7.7)	16/208 (7.7)
Hypertension (%)		629/1033 (60.9)	164/307 (53.4)	103/206 (50.0)
Dyslipidemia (%)		623/1033 (60.3)	157/306 (51.3)	51/206 (25.0)
Body mass index >30 (%)		222/1010 (22.0)	60/260 (23.1)	22/155 (14.2)
Excessive alcohol consumption[e] (%)		128/906 (14.1)	24/253 (9.5)	NR[f]
Ever smoked (%)		559/1035 (54.0)	118/308 (38.3)	67/209 (32.1)

IQR: interquartile range. iADL: instrumental activities of daily living (higher score denotes greater impairment). NR: not recorded.

[a] Can sit to stand once or more: cannot sit to stand.

[b] This was extrapolated from Snellen chart performance for SCS whereas OATS and MAS participants were asked about the adequacy of their vision.

[c] Ever sought medical attention for a head injury.

[d] Ever clinically diagnosed.

[e] Defined as >21 standard drinks per week (Livingston *et al.*, 2020).

[f] Alcohol consumption was coded differently in SCS but the majority (74.1%) of participants consumed alcohol a few times per month or less frequently.

5. Handling of missing data in predictors and covariates

Missing data ranged from 0% (age and sex) to 35.3% (wave 3 RAVLT) for the predictors and covariates. Multiple imputation using fully conditional specification was performed to impute missing values in predictors (i.e. the super-aging definitions) and covariates in each sample. Five imputed datasets were generated. The analyses were first conducted in each imputed dataset, and the results were then pooled using Rubin's rules (Rubin, 2004).

Results

The components of the nine super-aging definitions applied to the three samples are presented in Table 1. Demographic and clinical characteristics of the study participants are presented in Table 2.

1. Assessment of frequency of super-aging based on different published definitions and agreement between definitions

The frequency of super-aging status varied widely across the three cohorts based on the published definitions as detailed in Table 3. The lowest frequency was 2.9% for definition four: maintenance of verbal episodic memory scores at or above the median for adults in their 20s as well as a MMSE score of 29 or above over three waves of follow-up. The highest frequency was for definition eight which required performance in the top 50 percent of the sample or top 50 percent expected for age for those 90 and above on memory and executive function tests. Otherwise, frequency roughly paralleled the stringency of the classification with proportion of super-agers identified from largest to smallest: definition 8, 3, 2, 9, 5, 7, 1, 6, 4. The frequency of super-aging was generally much lower in the SCS cohort.

Inter-definition reliability assessed between each super-aging definition was highly variable as shown in Table 4. Levels of agreement for published definitions ranged from poor ($\kappa = 0.04$, CI 0.02–0.06; AC1 = 0.24, CI −0.10 to 0.58) for definitions 4 and 8 to very good for definitions 2 and 3 ($K = 0.83$, CI 0.79–0.87; AC1 = 0.91, CI 0.72–1.10). The large discrepancy between kappa and AC1 values is likely due to the low frequency of super-aging in our samples as kappa values are highly

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Table 3. Frequency of super-aging on the basis of nine published definitions

DEFINITION	OVERALL FREQUENCY	FREQUENCY IN MAS (N = 1037)	FREQUENCY IN OATS (N = 361)	FREQUENCY IN SCS (N = 217)
Cognition comparable to younger adults in ≥1 domain				
1	5.8% (n = 94)	8.4% (n = 87)	0.8% (n = 3)	1.8% (n = 4)
	14.3% of ≥ 80yo (n = 94/659)	21.2% of ≥ 80yo (n = 87/411)	9.7% of ≥ 80yo (n = 3/31)	
2	17.3% (n = 280)	18.5% (n = 192)	23.3% (n = 84)	1.8% (n = 4)
3	18.1% (n = 293)	19.4% (n = 201)	24.4% (n = 88)	1.8% (n = 4)
4	2.9% (n = 41/1398)	1.5% (n = 16)	3.3% (n = 25)	*No HVLT data past wave 1*
5	10.4% (n = 146/1398)	6.5% (n = 67)	21.9% (n = 79)	*Oral TMT-A only*
Superior cognition for age in ≥1 domain				
6	3.1% (n = 44/1398)	4.4% (n = 36)	2.5% (n = 8)	*No HVLT data past wave 1*
7	9.5% (n = 153)	10% (n = 104)	9.7% (n = 35)	6.5% (n = 14)
8	43.7% (n = 705)	49.5% (n = 513)	50% (n = 180)	5.5% (n = 12)
9	13.6% (n = 219)	13.6% (n = 141)	12.7% (n = 46)	14.7% (n = 32)

influenced by low prevalence. As expected, these differences were most pronounced for the definitions with the lowest frequency.

2. Association of super-aging status with daily function

The GLM results indicated significant associations between super-aging status (based on definitions 2, 6, and 8) and reduced functional impairment at baseline, while controlling for measures of physical health and sensory impairment (Table 5). However, after correcting for multiple testing using the Holm-Bonferroni method, none of these definitions remained significant. Super-agers had functional impairment scores ranging from 4.7 to 11% lower than their counterparts.

3. Association of super-aging status with structural brain imaging measures and burden of white matter disease

Whole brain volume, cortical volume, and hippocampal and caudal anterior cingulate volumes were generally higher in super-agers, though differences were only significant for definitions 2, 8, and 9 (Table 5). After correcting for multiple testing, only definitions 8 and 9 remained significant. All definitions were associated with a lower burden of white matter hyperintensities, ranging between 3.8 and 33.2% lower than in non-super-agers. This association was significant for four out of nine definitions (definitions 2, 3, 4, and 7) and only remained significant for definitions 2 and 3 after correcting for multiple testing

4. Association of super-aging status with incident dementia

In MAS, 105 participants were classified as having developed dementia over four waves of follow-up, 11 in OATS and 36 in SCS. Super-aging status was associated with a lower risk of dementia for definitions 1, 2, 3, 7, 8, and 9 but not for definitions 4, 5, and 6 (Table 5). Associations remained significant for definitions 2, 3, 7, 8, and 9 after correcting for multiple testing.

Discussion

We endeavored to add to the super-aging literature through a direct comparison of different definitions of cognitive super-aging within the same longitudinal cohorts. This has not been done previously. Despite some overlap in existing definitions of super-aging, the frequency of super-aging differed substantially depending on the definition used. Levels of agreement between various definitions ranged from poor to very good. Associations between super-aging status and functional status which also varied based on the definition used, were small but generally consistent.

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Table 4. Level of agreement between definitions

DEFINITION	2	3	4	5	6	7	8	9
1	**κ = .19** CI 0.13–0.25 AC1 = .75 CI 0.50–1.00	**κ = .20** CI 0.14–0.26 AC1 = .74 CI 0.49–0.99	**κ = −.03** CI −0.04 to −0.02 AC1 = .89 CI 0.87–0.91	**κ = −.03** CI −0.06 to −009 AC1 = .81 CI 0.58–1.04	**κ = .03** CI 0.03–0.09 AC1 = .91 CI 0.72–1.1	**κ = .14** CI 0.07–0.2 AC1 = .85 CI 0.64–1.06	**κ = .07** CI 0.04–0.1 AC1 = .22 CI −0.12 to 0.56	**κ = .02** CI −0.03 to 0.07 AC1 = .78 CI 0.53–1.03
2		**κ = .83** CI 0.79–0.87 AC1 = .91 CI 0.72–1.10	**κ = .18** CI 0.13–0.23 AC1 = .78 CI 0.54–1.02	**κ = .09** CI 0.03–0.15 AC1 = .68 CI 0.41–0.95	**κ = .21** CI 0.15–0.27 AC1 = .78 CI 0.54–1.02	**κ = .53** CI 0.47–0.58 AC1 = .84 CI 0.62–1.06	**κ = .26** CI 0.22 – 0.3 AC1 = .30 CI −0.02 to 0.62	**κ = .31** CI 0.25–0.37 AC1 = .75 CI 0.49–1.01
3			**κ = .19** CI 0.14–0.25 AC1 = .78 CI 0.54–1.02	**κ = .07** CI 0.01–0.12 AC1 = .66 CI 0.39–0.93	**κ = .22** CI 0.16–0.23 AC1 = .78 CI 0.57–0.99	**κ = .56** CI 0.50–0.62 AC1 = .85 CI 0.63–1.07	**κ = .26** CI 0.22–0.30 AC1 = .30 CI −0.02 to 0.62	**κ = .29** CI 0.23–0.35 AC1 = .73 CI 0.47–0.99
4				**κ = .05** CI −0.007 to 0.11 AC1 = .86 CI 0.65–1.07	**κ = .20** CI 0.08–0.32 AC1 = .94 CI 0.96–1.1	**κ = .27** CI 0.18–0.36 AC1 = .90 CI 0.71–1.09	**κ = .04** CI 0.02 – 0.06 AC1 = .24 CI −0.10 to 0.58	**κ = .14** CI 0.07–0.21 AC1 = .83 CI 0.60–1.06
5					**κ = .04** CI −0.01 to 0.09 AC1 = .86 CI 0.65–1.07	**κ = .10** CI 0.03–0.17 AC1 = .80 CI 0.57–1.03	**κ = .10** CI −.07 to 0.13 AC1 = .24 CI −0.09 to 0.57	**κ = .16** CI 0.09–0.22 AC1 = .77 CI 0.52–1.02
6						**κ = .44** CI 0.35–53 AC1 = .92 CI 0.74–1.1	**κ = .07** CI 0.05–0.09 AC1 = .24 CI −0.09 to 0.58	**κ = .17** CI 0.11–0.24 AC1 = .84 CI 0.61–1.07
7							**κ = .17** CI 0.14–0.20 AC1 = .30 CI −0.02 to 0.63	**κ = .37** CI 0.31–0.44 AC1 = .83 CI 0.60–1.06
8								**κ = .21** CI 0.17–0.25 AC1 = .33 CI 0.003–0.66

Kappa (κ): 0–0.20 = poor, 0.21 = 0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = good, 0.81–1.00 = very good [52], AC1 is interpreted similarly to kappa (Gwet, 2010), CI: 95% confidence interval.

Table 5. Association between super-aging status and outcomes

Association between super-aging status and function					
DEFINITION	ESTIMATE	STANDARD ERROR (SE)	EXPONENTIATION OF B	% CHANGE[a]	SIGNIFICANCE
1	$b = 0.013$	0.01	Exp(b) = 1.01	1.3%	$p = 0.772$
2	$b = -0.063$	0.03	Exp(b) = 0.94	− 6.1%	$p = 0.040$
3	$b = -0.048$	0.03	Exp(b) = 0.95	− 4.7%	$p = 0.106$
4	$b = -0.063$	0.06	Exp(b) = 0.94	− 6.1%	$p = 0.328$
5	$b = -0.050$	0.04	Exp(b) = 0.95	− 5%	$p = 0.153$
6	$b = -0.117$	0.05	Exp(b) = 0.89	− 11%	$p = 0.031$
7	$b = 0.008$	0.04	Exp(b) = 1.01	0.8%	$p = 0.834$
8	$b = -0.052$	0.03	Exp(b) = 0.95	− 5.1%	$p = 0.049$
9	$b = -0.059$	0.03	Exp(b) = 0.94	− 5.7%	$p = 0.083$

Association between super-aging status and structural imaging markers ($n = 751$)

DEFINITION	SUPER-AGERS MEAN VOLUME (SD)	NON-SUPER-AGERS MEAN VOLUME (SD)	ESTIMATE	SE	SIGNIFICANCE
Whole brain volume (ml)					
1[b]	998.71 (119.00)	1042.18 (105.34)	b = 13.94	15.82	$p = 0.378$
2	1043.86 (105.02)	1038.50 (106.76)	b = − 3.71	8.53	$p = 0.663$
3	1036.66 (103.27)	1041.31 (107.02)	b = − 2.42	8.85	$p = 0.785$
4	1014.98 (106.60)	1043.91 (106.54)	b = − 19.92	30.30	$p = 0.523$
5	1082.10 (94.36)	1037.28 (106.58)	b = 25.33	20.72	$p = 0.252$
6	1011.50 (101.83)	1043.62 (106.14)	b = 5.55	19.73	$p = 0.779$
7	1029.44 (101.17)	1041.00 (106.90)	b = − 0.08	11.34	$p = 0.994$
8	1054.41 (110.39)	1030.34 (99.66)	b = 19.90	7.30	$p = 0.006$
9	1055.69 (106.47)	1035.57 (106.64)	b = 26.11	9.82	$p = 0.008$

Cortical volume (ml)						
1	396.26 (40.98)		412.69 (39.10)	b = 6.56	5.84	$p = 0.261$
2	415.84 (39.44)		410.53 (39.16)	b = 0.67	3.16	$p = 0.832$
3	413.27 (38.55)		411.59 (39.37)	b = 0.89	3.29	$p = 0.787$
4	403.69 (38.23)		413.58 (39.27)	b = − 7.00	12.80	$p = 0.576$
5	426.66 (34.81)		411.28 (39.22)	b = 7.20	7.19	$p = 0.339$
6	409.17 (36.30)		413.20 (39.13)	b = 6.04	6.84	$p = 0.378$
7	412.06 (38.68)		411.71 (39.38)	b = 2.92	4.19	$p = 0.486$
8	418.72 (39.27)		406.97 (37.87)	b = 9.93	2.66	$p < .001$[c]
9	420.23 (38.63)		409.90 (39.22)	b = 11.55	3.63	$p = 0.001$[c]
Hippocampal volume (ml)						
1	7.00 (0.87)		7.33 (0.85)	b = 0.19	0.13	$p = 0.132$
2	7.54 (0.84)		7.24 (0.84)	b = 0.14	0.07	$p = 0.043$
3	7.49 (0.86)		7.26 (0.84)	b = 0.12	0.07	$p = 0.076$
4	7.47 (0.77)		7.33 (0.83)	b = 0.02	0.22	$p = 0.936$
5	7.66 (0.77)		7.31 (0.84)	b = 0.11	0.12	$p = 0.393$
6	7.50 (0.75)		7.34 (0.84)	b = 0.22	0.17	$p = 0.200$
7	7.45 (0.83)		7.29 (0.85)	b = 0.12	0.09	$p = 0.184$
8	7.46 (0.81)		7.18 (0.86)	b = 0.18	0.06	$p = 0.002$
9	7.51 (0.87)		7.26 (0.85)	b = 0.22	0.08	$p = 0.007$
Caudal anterior cingulate (ml)						
1	3.30 (0.66)		3.29 (0.58)	b = 0.15	0.10	$p = 0.123$
2	3.33 (0.57)		3.28 (0.59)	b = 0.05	0.05	$p = 0.396$
3	3.35 (0.59)		3.28 (0.59)	b = 0.08	0.06	$p = 0.168$
4	3.30 (0.53)		3.30 (0.60)	b = − 0.003	0.13	$p = 0.980$
5	3.42 (0.61)		3.27 (0.58)	b = 0.14	0.08	$p = 0.064$
6	3.50 (0.57)		3.29 (0.59)	b = 0.25	0.11	$p = 0.021$
7	3.31 (0.58)		3.29 (0.59)	b = 0.08	0.07	$p = 0.278$
8	3.34 (0.60)		3.25 (0.58)	b = 0.09	0.05	$p = 0.047$
9	3.32 (0.61)		3.28 (0.59)	b = 0.05	0.06	$p = 0.450$
White matter hyperintensity volume (ml)[d]						
1	5.33(6.33)	3.76 (4.56)	b = − 0.161	Exp(b) = 0.85	− 14.9%	0.14	$p = 0.241$
2	2.68 (2.48)	4.28 (5.67)	b = − 0.373	Exp(b) = 0.69	− 31.1%	0.07	$p < .001$[c]
3	2.79 (2.55)	4.17 (5.23)	b = − 0.271	Exp(b) = 0.76	− 23.7%	0.08	$p < .001$[c]
4	2.18 (1.10)	3.95 (4.51)	b = − 0.403	Exp(b) = 0.67	− 33.2%	0.19	$p = 0.034$
5	2.48 (3.09)	3.89 (4.50)	b = − 0.140	Exp(b) = 0.87	− 13.1%	0.11	$p = 0.218$
6	2.76 (2.68)	3.82 (4.50)	b = − 0.039	Exp(b) = 0.96	− 3.8%	0.20	$p = 0.847$
7	2.75 (2.55)	4.03 (4.82)	b = − 0.274	Exp(b) = 0.76	− 24%	0.10	$p = 0.005$
8	3.74 (3.73)	4.05 (6.24)	b = − 0.128	Exp(b) = 0.88	− 12%	0.07	$p = 0.058$
9	3.97 (4.32)	3.91 (4.76)	b = − 0.069	Exp(b) = 0.93	− 6.7%	0.09	$p = 0.418$

Association between super-aging status and incident dementia

definition	hazard ratio	95% CI	significance
1	0.48	0.22–1.05	$p = .065$
2	0.12	0.04–0.38	$p < .001$
3	0.10	0.02–0.41	$p = .002$[c]
4	0.0		$p = .951$[c]
5	0.0		$p = .951$
6	0.0		$p = .961$
7	0.08	0.01–0.54	$p = .010$[c]
8	0.21	0.12–0.36	$p < .001$[c]
9	0.21	0.07–0.63	$p = .005$[c]

Generalized linear modeling (GLM) with a gamma distribution and a log-link function is used for the association with functional status and with white matter hyperintensities as these data were skewed. GLM with normal distribution and identity link is used for other brain volume outcomes. The models control for study, number of prescribed medications, sit-to-stand scores, hearing and visual impairment, and age and sex. For definitions 4–6, the sample only includes MAS and OATS participants.

[a]Percentage increase or decrease in iADL scores and burden of white matter hyperintensities as predicted by super-aging status. If Exp(b) is lower than 1, then it is calculated as $(1 - \text{Exp(b)}) \times 100\%$; if Exp(b) is higher than 1, then it is calculated as $(\text{Exp(b)} - 1) \times 100\%$. The negative sign indicates percentage decrease.

[b]Note definition 1 was the only definition requiring super-agers to be ≥ 80, age was adjusted for in the GLM analyses.

[c]Effects remaining significant after using the Holm-Bonferroni method to correct for multiple testing.

[d]WMH volumes expressed as median (IQR).

Super-aging definitions can be categorized into three broad approaches, two cross-sectional and one longitudinal. Those definitions including adults aged 80 and older with comparable episodic memory performance to middle-aged adults have been argued to represent individuals who have resisted age-related cognitive decline (Gefen *et al.*, 2014; Rogalski *et al.*, 2019) as older adults who have reached this age and are functioning at this level would have a higher likelihood of maintaining their cognitive abilities (Borelli *et al.*, 2018). However, as maintenance of cognitive performance is not required, they may capture so-called super-agers who started from a higher cognitive baseline but are actually declining over time.

The cognitive domains selected to represent super-aging status have been limited. A minority of studies have incorporated superior performance in domains other than episodic memory (Baran and Lin, 2018; Bott *et al.*, 2017; Dominguez *et al.*, 2021; Maccora, *et al.*, 2020; Saint Martin *et al.*, 2017; Yu *et al.*, 2020). Given that diverse cognitive processes are vulnerable to age-related decline as well as the impacts of neuropathology, we argue that future studies should be more inclusive of a range of cognitive domains.

Few studies have incorporated maintenance of high cognitive performance over time into definitions and no single definition of super-aging requires only the absence of cognitive decline. This is a research gap. Practically speaking, preserving existing cognitive abilities has more relevance to older people (Teater and Chonody, 2020) than performing at a higher level than others their age or matching younger adults. Maintenance of cognitive capacity is linked to other aspects of aging well that are important to older people such as independence and being able to make health and lifestyle choices (Teater and Chonody, 2020). Studies that incorporate maintenance of cognition into super-aging definitions will lead to a better understanding of contributors to preserved function. However, such definitions cannot be used for cross-sectional studies. Comparison with a younger cohort partially resolves this issue but could still result in the inclusion of individuals who have been outliers from an early age but are actually declining cognitively. There is also value in comparing high and average cognitive function in larger samples of older adults to assess what factors contribute to these differences.

In our study, the stricter the definition applied, the lower the frequency of super-aging. Application of a definition involving comparable performance to much younger adults on a verbal episodic memory test over three waves of follow-up as well as preserved global cognition using a cognitive screening test produced the smallest sample. A 50th percentile cutoff for composite memory and executive function tests unsurprisingly produced the largest sample. The three definitions with a longitudinal component (4, 5, and 6) produced smaller samples. The frequency of super-agers also differed between studies using the same definitions. These differences were predominantly due to the differing demographics between the cohorts with the lowest proportion of super-agers in the oldest group (SCS). Differences between cohorts were attenuated for definitions involving superior cognition for age. Note that definition 8 classified those under 90 in relation to the remainder of the sample but those aged 90 and above according to the normative 50th centile which disadvantages the SCS population as published norms for the tests used only go up to age 89 (Brandt, 1991; Tombaugh, 2004).

Levels of agreement were highest between definitions which incorporated similar tests and cutoff scores. The highest agreement was for two definitions which employed a similar cutoff comparable to younger adults on delayed recall of a word list and the same cutoff for trails B. Definitions based upon superior cognition for age involved different cognitive domains, different cognitive tests, and different cutoffs with variability in frequency and level of agreement between definitions. The three definitions which incorporated maintenance of high cognitive performance over time produced very small samples but high levels of agreement (AC1). Duration of follow-up in these studies varied from three waves of follow-up over an average of 12 years, to a single follow-up assessment at an average 2.5 years and at least one follow-up visit with an average follow-up period 2.5 years respectively.

Super-aging was associated with better functional status according to all but two of the definitions. The strength of the association varied between definitions, and there was some relationship between the stringency of the definition and functional status. While high functional status could be considered a key outcome accompanying cognitive super-aging, associations were generally small. This could be because exceptional cognition does not improve functioning beyond normal cognition, because the Bayer Activities of Daily Living Scale tests ordinary daily activities rather than those requiring high-level cognitive ability or that there are other contributors to functional status not assessed in our analysis.

Super-aging status at baseline was associated with a lower incidence of dementia during the studies for definitions 2, 3, 7, 8, and 9 although only 152 individuals ultimately developed dementia. Associations with super-aging status using those definitions that required maintenance of high cognitive performance (definitions 4, 5, and 6) were not associated

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with lower dementia incidence. Notably a dementia diagnosis could only be made in individuals able to complete cognitive testing at follow-up which would affect these analyses and definitions 4-6 could only be applied to the MAS and OATS cohorts.

Imaging data were available for just under half of the participants. Associations between super-aging status and brain volumes were mostly non-significant. However, super-agers had a significantly lower burden of white matter hyperintensities than others in the same cohorts for definitions 2 and 3. This is consistent with previous super-aging studies (Harrison *et al.*, 2018; Kim *et al.*, 2020) and presents a promising avenue of further research given that white matter hyperintensities are associated with modifiable risk factors for dementia (Low *et al.*, 2022).

Conclusion

The study illustrates the influence of the choice of neuropsychological testing parameters and the ages of samples and comparator groups on the frequency of super-aging, the heterogeneity between existing definitions and the impact on outcomes of functional status, dementia diagnosis, and imaging markers of brain aging. There are limitations to our findings; specifically, not all published super-aging definitions could be applied to our cohort data as we did not have the same or comparable neuropsychological tests and we made some substitutions for a similar test when data for a single test was not available. While attempts were made to standardize imaging findings across the studies, OATS participants in particular were scanned at different centers and a proportion of these study participants were scanned using a lower-resolution machine, affecting the comparability of imaging data.

Cognitive "super-aging" is ultimately a statistical construct, and, unlike a disease state, there is no gold standard test or biomarker to confirm diagnosis. This may explain why definitions vary so widely. A better understanding is needed of the pathophysiology and genetics of these exceptional individuals who resist cognitive decline to develop more robust measures. In the interim, a clearer common language is needed to progress research in this important area.

Conflicts of interest

HB is or has been an advisory board member or consultant to Biogen, Eisai, Eli Lilly, Roche, and Skin2Neuron. He is a Medical/Clinical Advisory Board member for Montefiore Homes and Cranbrook Care.

Description of authors' roles

A. Powell designed the study, analyzed the data, and wrote the paper, B. Lam assisted with study design, statistical analysis, and interpretation, D. Foxe assisted with study design and choice and interpretation of neuropsychological testing, J. Close supervised study design and review and editing of the manuscript, P. Sachdev supervised study design and review and editing of the manuscript, H. Brodaty supervised study design and review and editing of the manuscript.

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Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/S1041610223000935.

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