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FEATURED ARTICLE

Cognition, function, and prevalent dementia in centenarians and near-centenarians: An individual participant data (IPD) meta-analysis of 18 studies

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Abstract

Introduction: There are limited data on prevalence of dementia in centenarians and near-centenarians (C/NC), its determinants, and whether the risk of dementia continues to rise beyond 100.

Methods: Participant-level data were obtained from 18 community-based studies ($N = 4427$) in 11 countries that included individuals ≥95 years. A harmonization protocol was applied to cognitive and functional impairments, and a meta-analysis was performed.

Results: The mean age was 98.3 years (SD = 2.67); 79% were women. After adjusting for age, sex, and education, dementia prevalence was 53.2% in women and 45.5% in men, with risk continuing to increase with age. Education (OR 0.95;0.92–0.98) was protective, as was hypertension (odds ratio [OR] 0.51;0.35–0.74) in five studies. Dementia was not associated with diabetes, vision and hearing impairments, smoking, and body mass index (BMI).

Discussion: Among the exceptional old, dementia prevalence remains higher in the older participants. Education was protective against dementia, but other factors for dementia-free survival in C/NC remain to be understood.

KEYWORDS
centenarians, dementia, education, exceptional longevity, prevalence, risk factors

1 | INTRODUCTION

The population of people aged 100 years and above has increased dramatically over the past few decades and is forecast to reach 2.2 million in the coming 30 years.[1] There are concerns about the potential impact of this exceptionally aging population, with increased rates of disease and disability, on health and social systems. An important concern is the increasing risk of dementia with age, with some questioning whether dementia is inevitable if one lives to an extreme old age.[2]

Examining the prevalence of dementia at the extreme of older adulthood, however, is challenging. Dementia is defined by deficits in multiple cognitive domains and a decline in functioning.[3] However, cognitive decline in extreme old age is difficult to ascertain owing to the lack of good normative data for this age group. Other factors might also hinder an accurate measurement of cognition in this population, including sensory and physical impairments, fatigue, medical comorbidities, low level of literacy, and attrition bias.[4] The published literature, which comprises ten prevalence studies of dementia in late older adulthood (i.e., aged over 95 years), suffers the constraints of small sample sizes, inconsistent methodologies, inadequate normative data, and the lack of a standardized protocol for dementia diagnosis.[5] While there are anecdotal reports of cognitively normal individuals aged over 110 years[6] more systematic analysis is needed.

Our primary aim was to obtain a better estimate of dementia prevalence in the very old population from around the world and explore risk and protective factors for dementia that are robust across ethno-regional groups. We combined data from 18 international studies of centenarians and near-centenarians (C/NC) that are part of the International Centenarian Consortium-Dementia (ICC-Dementia).[7]

2 | METHODS

2.1 | Description of the contributing studies and inclusion criteria

The 18 members of the consortium are studies of cognitive aging in community settings from 11 countries (see Table 1 for descriptive data

TABLE 1 Sample characteristics of participating studies

Study	Abbreviation	Location	*N*	Female	Mean age (SD)	Age range	Period of data collection	Sampling approach	Response rate	NOS rating (out of 7)[d]
90+ Study[32]	90+	California, USA	960	0.79	96.62 (2.27)	95–108	2003–2007	Population-based[c]	0.82	6
100-plus Study	100+	Amsterdam, Netherlands	102	0.74	101.10 (1.74)	98–110	2013–2015	Convenience sampling through online search[d]	Not published	5
Centenarians at Trieste[33]	CaT	Trieste, Italy	70	0.89	102.55 (1.89)	100–108	2014	Population-based[c]	Not published	6
Cognitive function and aging study	CFAS	England and Wales, UK	69	0.84	96.99 (2.05)	95–105	1991–1994	Population-based[c,d]	0.80	6
Fordham centenarian study[34]	FH	New York, USA	119	0.78	99.25 (2.50)	95–107	2010 – 2016	Population-based + volunteers[c]	0.23	6
Georgia centenarian study	GCS	Georgia, USA	239	0.82	100.15 (1.96)	98–109	1988–2009	Population-based[c]	0.19	6
Gothenburg centenarian study	Go95+	Gothenburg, Sweden	591	0.82	97.18 (.14)	96–98	1996–2015	Population-based[c]	0.65	6
2nd Heidelberg centenarian study[35]	HD100II	Heidelberg, Germany	112	0.89	100.45 (.47)	99–103	2011–2013	[c]Population-based + volunteers	0.30	6
Hong Kong centenarian study	HKCS	Hong Kong, China	152	0.78	97.68 (2.35)	95–108	2009–2011	Quota sampling[d]	0.30	6
Longevity gene project	LGP	New York, USA	109	0.71	98.16 (2.83)	95–110	1998–2014	Volunteers[d]	Not published	5
Monzino 80+ study	M80+	Varese province, Italy	501	0.71	98.54 (2.57)	95–106	2002–2010	Population-based[c]	0.96	6
Oregon brain aging study	OBAS[b]	Oregon, USA	120	0.65	95.35 (.65)	95–100	1989 – 2015	Volunteers[d]	Not published	5
Polish centenarian study	PCS	Katowice, Poland	89	0.80	100.94 (1.14)	99–105	2007–2015	Population-based[c]	0.08	6
Oporto centenarian study[36]	PT100	Porto, Portugal	140	0.89	101.18 (1.59)	100–108	2013–2015	Population-based[c]	Not published	6
Sydney centenarian study[37]	SCS	Sydney, Australia	343	0.72	97.41 (2.10)	95–106	2007–2014	Population-based[c]	Not published	6
Swedish centenarian study[38]	SwCS	Southern Sweden	99	0.82	101.94 (1.75)	100–109	1987–1992	Population-based[c]	0.70	6
Tokyo centenarian study[11]	TCS	Tokyo, Japan	304	0.79	101.14 (1.74)	100–108	2000–2012	Population-based[c]	0.26	6
Kurihara project[39]	KP	Kurihara, Japan	308	0.84	96.87 (1.93)	95–104	2010	Public health record[d]	1	6
All				0.79	98.25 (2.67)					
N			4427	3473						

Note: Population-based studies attempted to recruit their participants from the entire target population, while studies with convenience samples recruited from accessible sources, for example, volunteers from a medical centre.

[a]Values are the proportion of data to the sample unless specified.

[b]Only data from participants aged 95 and above at the earliest visit are included.

[c]Referred to as population-based studies. Referred to as studies with convenience samples.

[d]NOS refers to the Newcastle-Ottawa Scale for assessing the quality of cohort studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). As our analysis only involves baseline data, the last two questions under 'Outcome' of the scale is irrelevant. The highest possible rating is 7.

and Table S1 for each study reference). Inclusion criteria for studies were: (1) the whole or part of the sample comprised individuals aged 95 years and older with complete demographic data pertaining to age, sex, education, and medical history; (2) the assessment included measures of cognition and function; and (3) informed consent and ethics approval permitted the sharing of de-identified data with collaborators. Studies were approved by their respective institutional review boards, and the ICC-Dementia collaboration itself was approved by the University of New South Wales Human Research Ethics Committee (approval number: HC17956).

2.2 | Data harmonization

All contributing studies provided participant-level data from their first assessment wave. The Sydney team (YL, CD, JC, NK, HB, PS) processed, harmonized, and analyzed the data.

2.2.1 | Demographics

Age was recorded in years and categorized into three age groups: 95–99, 100–104, and ≥105. Age was also examined as a continuous variable. Most studies measured education in years, but some employed categories. Therefore, education was harmonized into three categories, taking into account the education system in each locale and the International Standard Classification of Education including: completed primary or less (≤7 years); high school completion or less (≤12 years); and, beyond high school (≥13 years) (see Table S1).

2.2.2 | Functional ability

Since studies used different instruments to assess function (Table S2), five common and compatible activities of daily living (ADL) items were chosen for harmonization – continence, feeding, dressing, mobility/transfer, and bathing (using the Katz ADL[8]), which are regarded as reliable measures of functional impairment in older adults (65–89 years old) across five European countries.[9] The ADL item scores were dichotomized, after clinical consensus, into two categories: independent (no assistance required, score = 1) and dependent (assisted by another person or device, score = 0). The sum of the five binary items provided an overall ADL score. We then created two binary variables representing impairment in daily functioning; one using liberal criteria for impairment (≥2 dependent ADLs = impaired), the other conservative (≥1 dependent ADL = impaired).

2.2.3 | Cognitive ability or status

Participating studies used a range of cognitive test instruments, the only common instrument being the Mini-Mental State Examination (MMSE), for which 12 studies provided item-level data (see Tables S3 to S6 and Figure S1). Clinicians regularly use a cutoff score of ≤23 for cognitive impairment/dementia,[10] but some studies have used lower cutoffs in centenarian populations to account for age and educational differences, that is, ≤22, ≤20, and ≤17. We derived optimal cutoffs for the MMSE by applying receiver operating characteristics (ROC) analyses to data from three studies (90+, SCS, and Go95+) where dementia diagnosis were arrived at by a consensus panel using established criteria based on a comprehensive neuropsychological test battery and the Diagnostic and Statistical Manual (DSM). Cutoffs obtained from the ROC analyses for the studies were ≤23, ≤21, and ≤20, respectively, which were consistent with the range of cutoffs used in previous research.[11,12] After considering both the cutoffs suggested by past literature and the current analysis, we decided to examine four criteria for cognitive impairment including MMSE scores ≤23, ≤22, ≤20, and ≤17.

Where studies (FH and HD100II) provided item-level scores based on the Short version of MMSE, equivalent cutoffs were calculated using a similar ROC analysis, but classifying cognitive impairment and dementia at different cutoffs including: ≤15, ≤14, ≤13, and ≤10. (See S3 for details).

2.2.4 | Medical history

Medical history data were contributed by a subset of the studies. Data includes the participants' body mass index (BMI), and whether

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed and found 12 studies of dementia prevalence in very late life (≥95 years) but with constraints of small sample sizes, inconsistent methodologies, inadequate normative data, and lack of a standardized protocol for dementia diagnosis. The prevalence ranged from 27% to 76% in these studies, being higher in women.
2. **Interpretation**: The prevalence of dementia continues to increase at the extreme end of life, from 38 (± 22.5)% at 95–99 years to 65(± 24.3)% at 100 years and above among women, and 34(± 33.1)% to 56(± 31.8)% among men. Functional impairment increases at an even faster rate than cognitive impairment. Education remains protective at this age, and hypertension is associated with lower risk, but other risk factors such as diabetes, sensory impairment, smoking, and body mass index (BMI) are not associated with dementia.
3. **Future directions**: The determinants of being non-demented as centenarians require further study if these exceptional individuals are to serve as models of successful aging.

they have a history of smoking, visual impairment, hearing impairment, hypertension, diabetes, and alcohol consumption. Hypertension was defined by either a history of clinical diagnosis, or based on the reading of their blood pressure at the point of data collection (criteria: systolic figure is higher than 140, or the diastolic figure is higher than 90, or both). From the BMI information, we conducted the analysis on whether being overweight (BMI ≥ 25) is a risk factor for dementia. Meta-analyses were conducted on hypertension, diabetes, overweight, hearing impairment, and visual impairment only, as it was not possible to harmonize the other variables due to the unstandardized measurement of the variable across the studies, or to perform the meta-analysis.

2.3 | Dementia diagnosis

A standard approach, which requires both cognitive and functional impairments, was used to define dementia. Dementia diagnoses were also provided by seven studies (90+, Go95+, M80+, SCS, PCS, CFAS, and OBAS); in five of these, (i.e., 90+, Go95+, M80+, SCS, and CFAS) diagnoses were consensus-based, one (OBAS) used the Clinical Dementia Rating and the last (PCS) used a structured interview (see Table S7). In HKCS, diagnoses relied on self-report or hospital diagnosis and therefore this was not included in our analyses for agreement between different approaches.

We did not require subjective cognitive complaints or concerns by others for the diagnosis, as these were not recorded by some studies and were regarded as redundant, given our observation that individuals in this age group invariably reported some decline from their previous level of cognitive functioning. Eight diagnostic criteria for dementia were therefore implemented based on the combination of the four cognitive and two functional performance criteria (Table 2).

TABLE 2 Combinations of cognitive and functional cutoffs used for the diagnosis of dementia

Criteria	MMSE cutoff	Dependent ADL
M17A1	≤17	≥1
M20A1	≤20	≥1
M22A1	≤22	≥1
M23A1	≤23	≥1
M17A2	≤17	≥2
M20A2	≤20	≥2
M22A2	≤22	≥2
M23A2	≤23	≥2

Abbreviations: ADL, activities of daily living[8]; MMSE, Mini-Mental State Examination.[3]

2.4 | Statistical approaches

The main analysis involved performing three sets of meta-analyses examining the association of age, sex, education, and residential status with the prevalence of dementia, cognitive, and functional impairments (as described above).

Before performing the meta-analyses, we imputed missing item data for the MMSE and ADLs, which were common across studies. Missing item data for the MMSE and ADLs was imputed using multiple imputations (with the *MICE* package in R, with number of imputations (m) = 30). The MICE package in R assumes that the missing data are missing at random. It predicts the the missing values based on the available data in the item using linear regressions. We did not impute data for participants missing more than 3 (out of 30; 10%) MMSE item scores or 1 (out of 5; 20%) ADL item score, and these participants were excluded from the analyses. According to {Jakobsen, 2017 #37@@author-year}, proportion of missing data over 40% is considered too large and inappropriate for imputation. Therefore, we have taken a more conservative approach.

After imputing missing MMSE and ADL data and calculating total scores, categorical variables were created for cognitive and functional impairment (normal = 0, impaired = 1), as well as for dementia (normal = 0, demented = 1) based on our eight diagnostic criteria for dementia described above.

For each of the eight dementia classifications, we assessed the level of agreement with dementia classifications provided by six studies using Cohen's kappa.

General linear logistic regressions were performed (R function 'glm', method = logit) with data from each study to examine independent associations between each of age, sex, and education and each of the diagnostic categories: four for cognitive impairment (one for each diagnostic criterion), two for functional impairment, and eight for dementia.

After performing logistic regression for each study, meta-analytic mixed-effects models (R function 'rma' in the *metafor* package) were applied using the coefficient and its standard error from the logistic regression models, treating studies as a random effect. It basically uses regression to combine and compare findings from multiple studies with the assumption that the studies are heterogeneous (see {Viechtbauer, 2010 #41@@author-year} for more details). The forest plots produced show the observed effect and the respective 95% confidence interval of each study and of the pooled result, as well as the I^2 statistics that reflect heterogeneity between studies. Studies with no participants in a level for a factor (e.g., no male with M17 criteria cognitive impairment) were excluded from the meta-analysis.

Adjusted prevalence rates presented throughout the paper were obtained from logistic regressions with dementia diagnosis as the outcome variable, and age, sex, and education as the predictors. The rates were adjusted to the mean age, mean years of education, and the proportion of women in the data set (harmonized or by study, depending on the information or Table) using the regression coefficients from the model(s).

All analyses were conducted using R (v.3.4.3).

3 | RESULTS

3.1 | Demographic characteristics of cohorts across studies

Table 1 shows the sampling strategies and demographic characteristics of each study. Sample sizes ranged from 69 to 960 participants. SwCS, GCS, and OBAS commenced data collection earliest (from 1987); CaT and PT100 started recruitment within the past 5 years. Most studies were conducted in the United States ($n = 5$) or Europe ($n = 9$), with only three studies conducted in the Asia-Pacific region, including Australia, Japan, and China. Twelve of the studies were population-based while six had used a convenience sampling approach (see Table 1). Reported response rates ranged from 0.08 to 0.88. There were more females than males in every study.

The distributions of age and education levels based on the harmonization protocol are presented in Table S8. Not all studies had participants in all age ranges. For instance, there were three studies with no participants < 100, while Go95+ had no participants over 100 years. Thirteen studies recruited participants aged 105 and above. Mean years of education varied, with participants in North America generally having higher education. In ten studies, more than half of the participants were living in the community at the time of data collection.

3.2 | Distribution of MMSE and ADL scores in individual studies and in the combined sample

The distribution of the MMSE and ADL total scores used to evaluate cognitive and functional performance, respectively, are presented in Table S3. The mean total MMSE scores ranged from 15.73 to 26.43, with a combined sample mean < 20. Across all studies, most participants were functionally impaired on > 2 ADL domains. Participants in GCS, HKCS, SCS, and FH had lower average impairment (≤2 domains) (Table S14).

3.3 | Prevalence of dementia, cognitive, and functional impairments

We measured the prevalences of dementia, cognitive and functional impairments based on the criterion with the highest agreement with consensus-based diagnoses (MMSE ≤22 and ≥1 impaired ADLs; that is, criteria M22A1, see next section), with rates adjusted to the mean age, years of education and the proportion of women participants in the combined data set.

Table 3 presents dementia prevalence in studies with different sampling approaches. In population-based studies ($n = 12$), dementia prevalence was 53.2 (± 23.5)% in women and 45.5(± 32.0)% in men overall, with 64.8 (± 24.3)% and 55.7(± 31.8)% in centenarian women and men, respectively. Mean prevalence of dementia was lower in studies with a convenience sample (about 29% overall and 31% in centenarians for both men and women) but with a larger range.

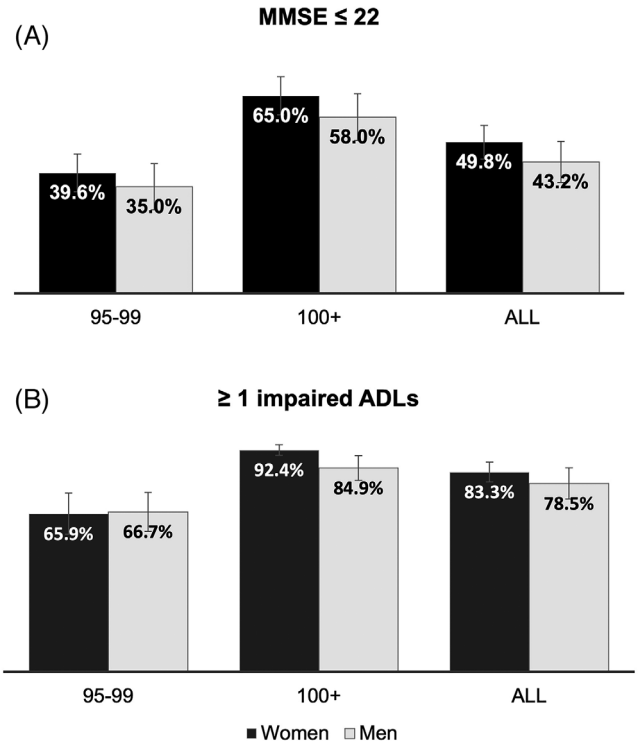

FIGURE 1 (A) Prevalence of cognitive impairment in population-based studies after adjusting for age, sex, and education across age groups. Note: Error bars represent standard errors of the mean (throughout). (B) Prevalence of ADL impairments in population-based studies after adjusting for age, sex, and education across age groups

Prevalences of cognitive (MMSE ≤22) and functional (≥1 impaired ADLs) impairments are presented in Tables S9 and S10, respectively. After adjusting for age and education, prevalence of cognitive impairment was 49.8 (± 19.2)% in women and 43.2 (± 23.5)% in men among population-based studies. The prevalence of cognitive impairment was 39.6(± 21.5)% and 35.0(± 26.3)% in near-centenarian (95–99 years old) women and men, and 65.0(± 21.9)% and 58.0(± 26.9)% in centenarian women and men, respectively. While the mean rates of cognitive impairment and dementia were under or around 50%, those of functional impairment were close to 80%. About 92% and 85% of centenarian men and women respectively from population-based studies were impaired in performing at least one ADL. Prevalence of dementia, cognitive, and functional impairments increased with age using the separate and combined MMSE and ADL criteria, as shown in Figures 1, 2, without any indication of leveling off after age 100.

3.4 | Agreement of above dementia classifications with those provided by each study

Table S7 presents Cohen's kappa coefficients indicating the level of agreement between dementia classifications obtained by our method and those provided by six studies. For the four studies that provided consensus diagnoses, the kappa coefficients ranged from 0.32 (fair

TABLE 3 Dementia prevalence of each study after adjusting for age, sex, and education (criteria: MMSE ≤22 and ≥1 ADL impairments)

Study		All		95–99		100+	
	N	Women	Men	Women	Men	Women	Men
Convenience samples							
100+	63	2.31%	4.38%	0.81%	1.56%	7.10%	12.88%
HKCS	139	22.96%	11.71%	23.46%	12.00%	22.43%	11.40%
OBAS	56	0.07%	0.02%	4.50%	1.55%	0.00%	0.00%
Mean		8.45%	5.37%	9.59%	5.04%	9.84%	8.09%
SD		12.62%	5.91%	12.15%	6.03%	11.46%	7.05%
Population-based							
90+	216	60.65%	28.99%	48.33%	19.86%	72.82%	41.51%
CaT	20	48.15%	100.00%	33.77%	100.00%	64.34%	100.00%
CFAS	11	89.10%	100.00%	80.67%	100.00%	94.50%	100.00%
FH	108	19.66%	10.58%	20.10%	10.85%	19.19%	10.30%
GCS	205	49.07%	43.87%	33.76%	29.25%	66.10%	61.26%
Go95+	207	88.94%	81.40%	20.07%	12.03%	99.73%	99.51%
HD100	82	31.08%	19.23%	21.89%	12.89%	43.28%	28.72%
M80+	327	66.14%	45.83%	58.69%	38.09%	73.53%	54.61%
PCS	89	36.25%	26.41%	9.93%	6.51%	77.74%	68.80%
PT100	70	32.55%	23.11%	32.02%	22.68%	33.13%	23.58%
SCS	178	37.39%	14.69%	26.63%	9.48%	50.89%	23.01%
TCS	277	78.91%	51.64%	74.97%	46.09%	82.72%	57.75%
Mean		53.16%	45.48%	38.40%	33.98%	64.83%	55.75%
SD		23.49%	32.00%	22.58%	33.09%	24.26%	31.83%

Note: Adjusted prevalence rates were obtained from the logistic regression model with dementia diagnosis as the outcome variable, and age, sex, and education as the predictors. Prevalence ratios were adjusted to the mean age, mean years of education, and the proportion of women in each study. *N* refers to the sample size with participants who had completed both the MMSE and ADL assessments (full sample sizes presented in Table 1).

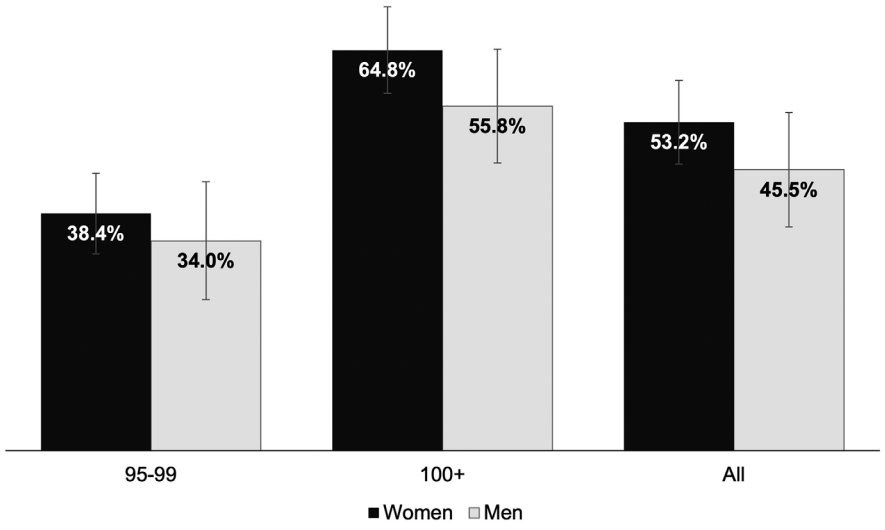

FIGURE 2 Dementia prevalence in population-based studies across age groups after adjusting for education. A logistic regression suggests that after controlling for sex and education, participants who aged 100 and over had significantly higher risk of dementia compared to those aged between 95 and 99 ($p < 0.001$)

agreement) to 0.88 (almost perfect agreement) across criteria and studies. The dementia criterion *M22A1* achieved the highest average agreement coefficient (0.73), although the range of values across criteria was not large (lowest 0.61) and several other criteria produced values of kappa only very slightly lower.

Figure S2 shows the reported rates of dementia based on consensus diagnosis, alongside rates of dementia based on the M22A1 criteria. The two sets corresponded very well, except for the 90+ study for which the consensus rate was approximately twice that according to the M22A1 criteria.

3.5 | Individual participant data meta-analyses

3.5.1 | Relationship with age, sex, and years of education

The pooled results of the logistic regression analyses examining the relationship between age, sex, and years of education with dementia, cognitive and functional impairments are shown in Table S11, model A. Pooled analyses indicated that all factors significantly predicted prevalence of dementia and cognitive impairment regardless of the criteria used. Prevalences of dementia and cognitive impairment were positively associated with age and female sex, and negatively correlated with years of education. Functional impairment was significantly associated with age and sex, but not education level (Figures S3, S5).

3.5.2 | Relationship with residential status

The pooled results of the logistic regression analyses examining the relationship of residential status with dementia, cognitive and functional impairments are shown in Table S11, model B. The pooled effects of residential status after controlling for age, sex, and education are shown in Table S12, model C. Residential status was significantly associated with dementia, cognitive and functional impairments in both models across criteria. Participants who were institutionalized were more likely to be have dementia or be cognitively or functionally impaired than participants living in the community (Figure S4, S6).

A higher level of heterogeneity ($I2 > 60\%$) across studies was observed for the association of education and residential status with dementia, while the effects of age and sex on dementia and impairments were relatively homogeneous (see Figure 3).

3.5.3 | Relationship with medical history, BMI, smoking, and sensory impairment

We performed additional analyses with studies that had provided data on the history of hypertension, diabetes, visual and hearing impairments, smoking, and the participants' height and weight. BMI was calculated and participants who had a BMI ≥ 25 were classified as being overweight. Descriptive statistics of the data included in the analysis can be found in Table S13. Results from the meta-analyses suggested no significant relationships of these variables with dementia risk except for hypertension (OR 0.51; 95%CI 0.35–0.74), data for which were available in five studies (GCS, Go96plus, PCS, SCS, and TCS) (Figure S7).

4 | DISCUSSION

This is the first and largest study to bring together numerous cohorts of C/NC internationally and harmonize the data to examine the global prevalence of dementia, and cognitive and functional impairments using a uniform set of diagnostic criteria. Our meta-analyses also enabled us to investigate heterogeneity in the effects of established risk and protective factors for dementia including age, sex, education, and some medical risk factors across 11 countries.

The diagnostic criteria used to classify dementia in this study are consistent with commonly used criteria. By applying a range of cutoffs derived from the sensitivity analyses, some of which were more liberal than those commonly used in younger older adult cohorts, we expect to have captured more sensitive estimates of dementia prevalence in this age group by allowing for age-related impairments. Nonetheless, the overall results for the risk and protective factors for dementia and impairments were similar across criteria.

After examining a range of cutoffs using sensitivity analyses, we presented results based on the criteria that had the highest agreement with consensus-based diagnosis (M22A1). Our results indicated that dementia prevalence was less than 10% in studies with convenience samples and around 50% in population-based studies, indicating that close to half of the global 95+ population live without dementia. Our estimated prevalence is lower than some of the previously reported rates, such as 76% and 85%,[13,14] but the heterogeneity in the rates across studies is similar to that reported previously. Such diversity of prevalence might be due to different sample sizes and sampling strategies (i.e., total population vs. convenience) used by individual studies.[11] Other factors such as health factors and/or ethno-racial differences might also play a role.

The results highlight that the risk of dementia increases significantly with age, from about 38% at 95 to 99 years to about 65% at 100 years and above among women, 34% to 56% among men. This supports previous reports of an exponential increase in dementia prevalence in the very old. Our finding that dementia prevalence does not stabilize after 95 years of age does not support the speculation that the prevalence of dementia reaches a plateau in extreme old age.[2,15,16] Prevalence of cognitive and functional impairments continues to increase with age, with functional impairment being more prominent. Centenarians also showed a larger variability in prevalence compared to near-centenarians.

There has been some discussion on what is 'normative cognition' for this age group, and whether such normative data should be used to determine dementia prevalence. While it is customary in the neuropsychological literature to use age and education-adjusted norms for the categorization of impairment, we argue that cognitive decline seen in the majority of individuals in this age group should not be

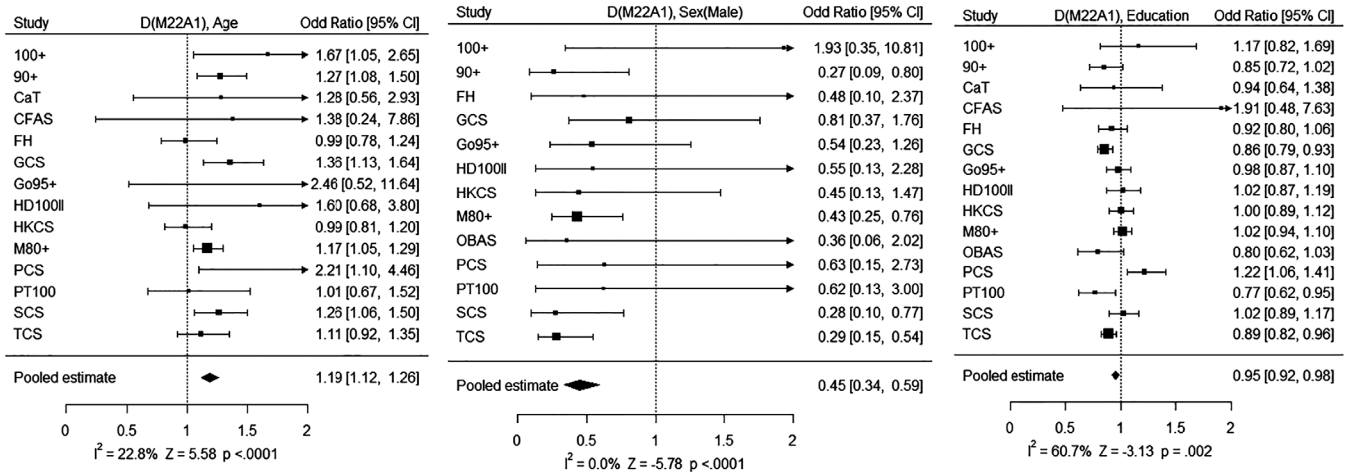

FIGURE 3 The relationship of age, sex, and education (Model A) with dementia based on the criteria of M22A1

necessarily seen as 'normal aging'. The approach we take is that any cognitive decline, irrespective of age, is of concern, and if it is severe enough to impair functional independence, it should be categorized as dementia. Moreover, the decline does not occur uniformly across all cognitive domains. Some studies[17,18] have suggested that centenarians perform similarly as younger age groups on naming, repeating, and listening and obeying regardless of visual or literacy deficits, but worse on tasks of verbal and nonverbal memory, psychomotor/executive performance, and category verbal fluency. Another caveat is that cognitive and functional performance can be influenced by the high prevalence of sensory loss, disability, and medical comorbidities in this age group,[13,19] which lessens the accuracy of dementia diagnosis unless more detailed medical records are available. It might be more meaningful, therefore, to refer to the prevalence of cognitive and functional impairments rather than dementia per se.

While there were more women than men in the sample, the meta-analysis indicated significantly higher dementia and impairment prevalences in women. This is consistent with findings from past centenarian studies and meta-analyses[12,20,21] that show that dementia risk is higher in women and that men have significantly higher MMSE total scores. It has also been argued that the risk factors for progression from mild cognitive impairment (MCI) to AD are different between men and women in their 60s and 70s.

Past literature strongly suggests that educational attainment is a protective factor against dementia.[22] Our study shows that education continues to be associated with lower risk of dementia and cognitive impairment into the 11th decade of life. It is important to note that the effect of education was more heterogeneous relative to age and sex. This could be due to the variation of educational opportunities and social resources across geographical regions and cultures, especially in early 20th century which was the formative period for these individuals.

While mid-life hypertension has been consistently linked with poorer cognition later in life,[23] the association of late-life hypertension with dementia is more complex and the data inconclusive.[24] Some studies have reported hypertension as being protective against dementia in the very old[25,26] as was seen in our analysis of five studies with the somewhat consistent finding of higher rates of hypertension in those not demented. The mechanisms underlying this association are unclear. It is possible that late-life hypertension is unrelated to a disease process that arguably begins decades before the clinical manifestations, or that higher blood pressure is protective in maintaining cerebral perfusion, rendering the brain less vulnerable to ischemic insults. There is also evidence that dementia may be related to a drop in blood pressure, thereby suggesting a reverse causality for this association.[25]

It is noteworthy that factors such as diabetes, vision and hearing impairments, smoking, and BMI were not significantly associated with dementia in this age group. It has previously been shown that the recognized risk factors for dementia in the 65–85 years population are not significant for the very old. Risk factors such as hypertension, diabetes, dyslipidemia, and smoking were not significant in the Leiden 85-Plus[27] and the Vantaa 85+[28] studies. The recent 100+ study in a Dutch population[29] found no difference in history of heart disease, hypertension, stroke, or diabetes in those who declined over 2 years and those who did not. It is possible that vascular risk factors pose the greatest risk in mid-life and produce cumulative risk over several years. Centenarians either develop these conditions later in life (so-called *delayers*) or have resilience to them (so-called *survivors*).[30] Alternatively, the accumulation of multiple pathologies in very old brains could reduce the association with risk factors for particular pathologies.[31]

Data harmonization in this study posed several challenges. It involved understanding the data collection and processing procedure of each study before developing a harmonization protocol. Besides variations in methodologies implemented across studies, such as different versions of MMSE and ADL measurements, there were issues relating to discrepancies in data availability which limited the scope of analysis such as adjusting for incidence and mortality rates. The influence of the level of representativeness of the studies on dementia prevalence needs to be further examined. From the current observation, a relatively homogenous representation of their cohort was offered by the population-based studies. Studies with convenience samples (e.g., 100+, HKCS) which recruited their

participants within the same state or city showed only small variations in their sample's age and years of education. While the harmonization process was time intensive, the combined dataset will facilitate future projects that require data sharing among members of the consortium.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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