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Psychosocial risk factors for dementia and brain age: A systematic review

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Systematic Review

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Abstract

Psychosocial factors are linked to increased dementia risk, potentially via accelerated brain ageing. Accelerated brain age, where estimated brain age exceeds chronological age, can be estimated using neuroimaging, epigenetic, and transcriptomic approaches. This systematic review examined associations between psychosocial risk factors (depression, anxiety, post-traumatic stress disorder [PTSD], psychological stress, social isolation, loneliness, neuroticism) and brain age in cognitively unimpaired adults, and whether associations differ by severity (clinical cases, symptoms) and age group (early-, middle-, older-adulthood). After screening, 44 studies were included. Findings were narratively synthesized due to heterogeneity. For depression (*k* = 32), relationships with brain age were mixed in early-adulthood (cases: 5 of 8 studies [5/8], symptoms: 3/7) and middle-adulthood (cases: 8/12, symptoms: 2/7), with most studies observing no association in older-adulthood (cases: 1/2, symptoms: 1/5). Anxiety (*k* = 5) was associated in early-adulthood (cases: 1/1, symptoms: 2/2) but not middle-adulthood (symptoms: 0/3). PTSD (*k* = 4) was not associated in early-adulthood (cases: 0/1, symptoms: 0/1) but associations were evident in middle-adulthood (cases: 2/3). Psychological stress (*k* = 4) showed mixed findings across early-adulthood (1/2) and middle-adulthood (1/2). Social isolation (*k* = 2) was consistently associated in middle-adulthood (2/2), whereas loneliness (*k* = 4) was mixed (1/3) and no association in early-adulthood (0/1). Neuroticism (*k* = 4) showed no associations across age groups (0/4). Evidence suggests some psychosocial risk factors are associated with brain age, which varies by risk factor, age group and severity. Research in older-adulthood is limited, yet brain ageing is observed in early- and middle-adulthood. Research is needed to establish whether psychosocial health interventions can modify brain ageing trajectories.

1. Introduction

Dementia is characterised by progressive cognitive deterioration, with Alzheimer's disease (AD) being its leading cause.(1) Given the projected global increase in dementia cases to 139 million by 2050, its prevention or delay is a public health and research priority.(1–3) Targeting modifiable risk factors and identifying critical periods of influence is key. Systematic reviews and meta-analyses have identified psychosocial risk factors for dementia including depression, anxiety, post-traumatic stress disorder (PTSD), psychological trauma, psychological stress, neuroticism, loneliness and social isolation;(4–10,3) however, the biological mechanisms linking them with dementia remain unclear. One mechanism may be via accelerated brain ageing. While chronological age (the largest dementia risk factor)(3) represents the number of years lived, biological age is an estimate of ageing-driven biological changes such as molecular and cellular degradation.(11) Given that ageing processes differ across organ systems, organ-specific biological age estimations have been developed.(12) In the context of dementia, brain age may be a more sensitive metric than chronological age to capture neurobiological ageing processes.(13) The difference between brain age and chronological age, broadly termed the brain age gap (BAG), has been associated with worse cognition in cognitively intact populations(14), is greater in individuals with dementia, and is associated with AD pathology.(14–16) BAG can capture cumulative, whole brain change, whereas single dementia biomarkers represent one pathway or structure(17).

Neuroimaging-based brain age estimation tools use machine learning models, trained algorithms (e.g., relevance vector regression) and input data (e.g. subcortical volumes) to produce a brain age metric estimate (e.g., BAG).(14,18) These tools have been applied across modalities, including structural magnetic resonance imaging (sMRI), functional magnetic resonance imaging (fMRI), electroencephalogram (EEG) and fractional anisotropy (FA).(19–21) Brain age can also be estimated using epigenetic clocks (DNA methylation [DNAm]), transcriptomic clocks (gene expression), and proteomic clocks (proteomic biomarkers).(11,22–24)

Four systematic reviews have investigated associations between psychological factors and brain age, with three reporting a higher BAG in depression and one finding mixed relationships.(25–28) Notably, in one review which examined schizophrenia and bipolar, BAG was sensitive to phenotypic differences in psychiatric disorders.(25) However, these reviews focused exclusively on neuroimaging studies and included just one anxiety and one PTSD study, leaving other psychosocial risk factors (e.g., loneliness) unexamined. None approached brain age from a dementia risk perspective, and individuals with cognitive impairment were included, potentially confounding findings. Although one review reported greater BAG in older versus younger individuals with mood disorders, others did not consider life stage.(25) A life stage approach, encompassing early-adulthood (age 18–39), middle-adulthood (age 40–64), and older-adulthood (age 65+), is crucial to understand critical windows of influence as highlighted by Livingston et al. (2024) and others.(3,29,30)

The current review aimed to address these gaps by conducting a comprehensive systematic review investigating the association between psychosocial risk factors for dementia (depression, anxiety, psychological trauma, PTSD, psychological stress, social isolation, loneliness, neuroticism) and brain age (using any approach) across the life course.

2. Method

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and was registered on PROSPERO (CRD420251016652).(31) **Supplementary table 1** contains the PRISMA checklist.

2.1 Literature Search

Five databases (Embase, Medline, PsycINFO, Web of Science, and Scopus) and MedRxiv (to identify preprint 'grey' literature) were systematically searched from inception to March 26, 2025.(32,33) Reference lists of the existing reviews and of included articles were examined.

2.2 Search Strategy

Supplementary tables 2A-F contain the full search strategy. Briefly, search terms were selected based on relevant existing reviews, background research and team meetings (ST, LM, HDK, NLM). The strategy consisted of two components related to 1) brain age and 2) psychosocial factors: depression, generalised anxiety, psychological stress/trauma, PTSD, social isolation, loneliness or neuroticism. In databases which allowed, MeSH terms supplemented the search. No restrictions were placed on language or publication date.

2.2 Study Selection

Covidence was used to facilitate screening (https://www.covidence.org/). Two researchers independently conducted title/abstract screening (ST: 100%; SE: 20%). Full-text screening followed the same approach, with reasons for exclusion recorded. Disagreements at either stage were resolved with a third reviewer (HDK). A pre-specified inter-rater agreement of $\kappa = .61$ (substantial agreement) was needed at each stage for the first screener to proceed with screening the remaining 80%.(34) Corresponding authors were contacted if articles were unobtainable or additional information was required.

Eligible studies met the following criteria (**supplementary table 3** contains full details):

1. Included cognitively unimpaired adults (mean age ≥ 18 years).
2. Reported psychiatric diagnosis using internationally recognised criteria or a standardised assessment of psychosocial factor(s) of interest. A control group was not mandatory, but if included it was required to be a healthy control comparator or report data separately for the group with psychosocial risk factor(s).
3. Estimated brain age using a brain-specific age tool (e.g., neuroimaging models, brain-specific epigenetic clocks).
4. Quantitatively analysed a cross-sectional or longitudinal association between brain age and psychosocial factor(s).

2.3 Data extraction

Standardised forms were developed and piloted to extract (1) study characteristics, (2) results and (3) details of brain age tool used (**see supplementary tables 4A-C**). Forms one and two were completed independently (ST: 100%; VM/ML: 100%), with discrepancies resolved through discussion and a third reviewer (NLM). Data for the third form were extracted by ST (100%).

2.4 Quality appraisal

A modified version of the Newcastle-Ottawa Scale, which considers selection, comparability and outcome criteria, was used to assess the quality of cross-sectional and longitudinal studies. (35,36) Study quality was independently assessed by two reviewers (ST: 100%; ML/VM: 100%), with discrepancies resolved through discussion and a third reviewer (NLM).

2.5 Data synthesis and analysis

Study characteristics, psychosocial factors, and brain age tools were synthesised using numbers and percentages for categorical variables, and medians for continuous variables. Studies reporting data from overlapping cohorts were identified to avoid over-representation.

A narrative synthesis was conducted by grouping studies first by psychosocial risk factor and severity (e.g., depression: cases and symptoms), then by age group (early-adulthood [18–39 years]; middle-adulthood [40–64 years]; older-adulthood [65 + years]) and finally by study design (cross-sectional vs longitudinal). Findings from adjusted models were reported whenever possible.

3. Results

3.1 Study selection

The literature search yielded 7,273 articles, with 2,966 remaining after deduplication. Following title/abstract screening 83 articles were retained for full-text review, with 40 articles finally included (**See** Fig. 1). Inter-rater reliability was substantial at title/abstract screening, $\kappa = .66$ and perfect at full-text review, $\kappa = 1.00$.

3.2 Study characteristics

Forty articles reported findings from 44 studies. Their characteristics are summarised in Table 1 and results in Table 2. Most studies were conducted in North America (*k* = 20, 45.5%); followed by Europe (*k* = 13, 29.5%), Asia (*k* = 5, 11.4%), Oceania (*k* = 2, 4.5%), and intercontinentally ([North America, Europe, Asia, Oceania, South America, and Africa] *k* = 4, 9.1%). Forty studies were cross-sectional (90.9%) and four were longitudinal (9.1%). The sample size ranged from 26 to 37,102 participants (median: 299.5).

Table 1
Overview of studies included in narrative synthesis

Author, year	Cohort, Country	Population	N	Age (SD)	Female, N (%)	Ethnicity / race, N (%)	Education years (SD)	Psychosocial risk factor(s) (Measure)†	Brain age tool modality
Abram et al.(72), 2023	University of California, US	HC	54	33.72 (NR)	12 (22%)	NR	15.38 (2.0)	Psychological stress (PSS)	sMRI
Ballester et al.(37), 2023	CAN-BIND, Canada	MDD	199	34.94 (12.63)	128 (64.3%)	NR	NR	MDD cases (DSM-IV-TR and MADRS ≥ 24)	sMRI
		HC	110	32.88 (10.70)	70 (63.6%)	NR	NR		
Ballester et al.(38), 2021	CAN-BIND, Canada	MDD	160	35.68 (12.60)	100 (62.5%)	NR	NR	MDD cases (DSM-IV-TR and MADRS ≥ 24)	sMRI
		HC	111	33.05 (10.78)	71 (64%)	NR	NR		
Besteher et al.(58), 2019	University of Jena, Germany	MDD	38	45.65 (15.68)	21 (55%)	NR	NR	MDD cases (DSM-IV)	sMRI
		HC	40	42 (13.17)	20 (50%)	NR	NR		
Christman et al.(60), 2020	Duke University Medical Centre, US	MDD	76	36.21 (9.04)	53 (68.4%)	Minority, 31 (40.8%)	15.34 (2.43)	MDD cases (DSM-IV-TR MINI v5.0 and MADRS ≥ 15)	sMRI
		HC	94	30.14 (9.2)	58 (61.7%)	Minority, 47 (50%)	15.69 (2.06)		
	Vanderbilt University Medical Centre, US	MDD	118	66.41 (5.45)	72 (61%)	Minority, 12 (10.2%)	16.79 (2.21)	MDD cases (DSM-IV-TR MINI v5.0 and MADRS ≥ 15)	
		HC	36	70.06 (6.65)	20 (55.6%)	Minority, 4 (11.1%)	17.17 (1.93)		

Author, year	Cohort, Country	Population	N	Age (SD)	Female, N (%)	Ethnicity / race, N (%)	Education years (SD)	Psychosocial risk factor(s) (Measure)[†]	Brain age tool modality
Clausen et al. (52), 2022	ENIGMA-PGC PTSD Consortium, Netherlands, China, US, Belgium, Canada, Germany	PTSD	884	35.9 (10.9)	410 (46.4%)	White, 465 (52.6%)	NR	PTSD cases (CAPS-4 ≥ 40 or CAPS-5 ≥ 23 or PCL-C ≥ 45 or PCL-M ≥ 45 or PCL-5 ≥ 23 or DTS ≥ 40 or SCID or MINI); PTSD severity within PTSD (CAPS-4 or CAPS-5 or PCL-C or PCL-M or PCL-5 or DTS or SCID or MINI)	sMRI
		HC	1,347	35.4 (11.0)	569 (42.2%)	White, 752 (55.8%)	NR		
Constantinides et al.(48), 2024	ALSPAC SCZ-RbG sub-study, UK	HC	189	22.71 (0.78)	101 (53.4%)	White, 189 (100%)	University level, 115 (79.3%)[a]	Depressive symptoms (sMFQ)	sMRI
									sMRI
Dai et al.(56), 2025	COI, HUH, HRC, HKH, UTO, Japan	MDD	239	42.69 (12.19)	114 (47.7)	NR	NR	MDD cases (DSM-IV-TR/ DSM5 using MINI)	sMRI
		HC[b]	439	41.40 (16.34)	261 (59.5%)	NR	NR		
De Lange et al. (39), 2021	UKBB, UK	HC	24,867	63.86 (7.51)	12,440 (50.0%)	White, 24,236 (97.5%) Black, 138 (0.6%) Mixed, 110 (0.4%) Asian, 214 (0.9%) Chinese, 62 (0.3%) Other, 107 (0.4%)	University degree, 12,406 (49.9%) A levels or equivalent, 3,378 (13.6%) O levels or equivalent, 5,469 (22.0%) NVQ or equivalent, 1,256 (5.1%) Professional qualification, 1,154 (4.6%) None of the above, 1,213 (4.9%)	Loneliness (responded yes); social isolation (score ≥ 2); neuroticism (EPQ-R-S); depressive symptoms (PHQ)	sMRI

Author, year	Cohort, Country	Population	N	Age (SD)	Female, N (%)	Ethnicity / race, N (%)	Education years (SD)	Psychosocial risk factor(s) (Measure)[†]	Brain age tool modality
Dintica et al. (67), 2023	CARDIA, US	Total	649	30.2 (3.4)	341 (52.5%)	Black, 267 (41.1%)	14.2 (2.2)	Depressive symptoms (CES-D)	sMRI
		Low symptoms	230	30.3 (3.5)	122 (53.0%)	Black, 80 (34.8%)	14.7 (2.2)		
		Medium symptoms	211	30.4 (3.4)	118 (55.9%)	Black, 76 (36.2%)	14.2 (2.2)		
		High symptoms	208	30 (3.4)	101 (48.6%)	Black, 111 (53.1%)	13.5 (2.1)		
Dunlop et al. (19), 2021	NKI, WCM, TWH, US	HC and MDD	848	49.45 (19.42)	538 (63.4%)	NR	NR	MDD cases (DSM-5 and HDRS > 17); depression severity within MDD (HDRS-17)	fMRI
		MDD	112	38.88 (11.76)	72 (64.3%)	NR	NR		
Franke et al. (63), 2013	SAFE, US	HC	185	64.9 (8.3)	91 (49.2%)	NR	NR	Depressive symptoms (GDS)	sMRI
Han et al.(43), 2022	ENIGMA MDD working group[c], Germany, Sweden, South Africa, Spain, Japan, France, Netherlands, Russia, Singapore, Turkey, US	MDD	766	39.82 (12.70)	498 (65%)	NR	NR	MDD cases (ICD-10, DSM-IV, MINI, DSM-IV-TR, CIDI or SCID); depression severity within MDD (BDI, HDRS); depression severity in MDD and HC combined (BDI, HDRS)	sMRI
		HC	751	38.80 (12.89)	499 (66%)	NR	NR		
Han et al.(44), 2021	ENIGMA MDD working group[d], Spain, Germany, Scotland, England, Ireland, US, Canada, Australia, Brazil	MDD	2,675	43.08 (13.68)	1,689 (63.1%)	NR	NR	MDD cases (Diagnostic interview); depression severity within MDD (BDI-II, HDRS-17)	sMRI
		HC	2,126	40.99 (15.64)	1,199 (56.4%)	NR	NR		

Author, year	Cohort, Country	Population	N	Age (SD)	Female, N (%)	Ethnicity / race, N (%)	Education years (SD)	Psychosocial risk factor(s) (Measure)†	Brain age tool modality
Han et al.(54), 2021	NESDA, Netherlands	MMD and/or anxiety	220	37.37 (10.20)	152 (69%)	NR	12.39 (3.19)	MDD and/or anxiety disorder cases (CIDI version 2.1); depression severity within MDD (IDS); anxiety severity in anxiety disorder plus HC (BAI)	sMRI
		HC	65	40.81 (9.78)	42 (65%)	NR	14.28 (2.86)		
Han et al.(53), 2021	Affiliated Hospital of Zhengzhou University, China	MDD	195	18.14 (4.47)*	100 (51.3%)	Chinese, 195 (100%)	10.11 (2.13)	MDD cases (DSM-4); depression severity within MDD (HDRS)	sMRI
		HC	130	21.25 (5.33)*	71 (54.6%)	Chinese, 130 (100%)	13.56 (4.50)		
Han et al.(57), 2018	Victorian Brain Bank Network, Harvard Brain Bank, Netherlands Brain Bank, and Stanley Medical Institute, Australia, US and Netherlands	MDD	74	54.12 (20.13)	32 (43.2%)	NR	NR	MDD cases (Psychiatrist determined using informant-reported information)	Brain tissue in Brodmann area 10 and Brodmann area 25
		HC	67	57.03 (17.13)	28 (41.8%)	NR	NR		
Jawinski et al.(50), 2022	BASE-II, Germany	HC	335	70.5 (3.8)	127 (37.9%)	NR	14.05 (2.88)[e]	Depressive symptoms (GDS, CES-D)	sMRI
Jha et al. (61), 2023	EMBARC, US	MDD	290	37.1 (13.2)	192 (66.2%)	Black, 56 (19.3%) Other, 45 (15.5%) White, 189 (65.2%)	NR	Depression severity within MDD (SCID and QIDS-SR ≤ 14, HDRS-17)	sMRI

Author, year	Cohort, Country	Population	N	Age (SD)	Female, N (%)	Ethnicity / race, N (%)	Education years (SD)	Psychosocial risk factor(s) (Measure)[†]	Brain age tool modality
Karim et al. (49), 2025	REMBRANDT, US	MDD	102	67.0 (4.55)	74 (72.5%)	White, 88 (86.3%)	15.8 (2.39)[f]	MDD cases (DSM-5 using MINI and MADRS ≥ 15)	sMRI
		HC	43	66.6 (5.39)	21 (48.8%)	White, 31 (72.1%)	16.7 (2.04)		sMRI
Karim et al. (62), 2021	FINA, US	MDD/GAD and HC	78	61.2 (8.5)	53 (68%)	White, 63 (81%) Black, 13 (17%) Hawaiian or Pacific Islander, 1 (1%) Mixed race, 1 (1%)	15.6 (2.6)	Anxiety symptoms (HARS), depression severity in MDD plus HC (MADRS), neuroticism (NEO-FFI), psychological stress (PSS)	sMRI
Koutsouleris et al.(45), 2014	Ludwig-Maximilian University, Germany	MDD	104	42.3 (12.0)	52 (50%)	NR	10.8 (1.7)	MDD cases (DSM-IV); depression severity within MDD (HDRS)	sMRI
		HC	437	32.6 (10.9)	214 (49%)	NR	12.2 (1.3)		
Kuo et al. (59), 2020	TANMIND, Taiwan	MDD	30	61.5 (8.2)	17 (56.7%)	NR	11.1 (4.3)	MDD cases (SCID for DSM4); depression severity within MDD (HDRS-17)	sMRI
		HC	109	62.0 (7.6)	57 (52.3%)	NR	8.7 (5.0)		
Lay-Yee et al. (73), 2023	DMHDS, New Zealand	HC plus isolated	855	45 (NR)	425 (49.7%)	NR	NR	Social isolation (2-items of RCS for childhood isolation and response to 'seems lonely' on an informant reported questionnaire NR for adult isolation)	sMRI
		HC	623	45 (NR)	NR	NR	NR		
		Child-only isolation	121	45 (NR)	NR	NR	NR		
		Adult-only isolation	80	45 (NR)	NR	NR	NR		
		Child-adult isolation	31	45 (NR)	NR	NR	NR		

Author, year	Cohort, Country	Population	N	Age (SD)	Female, N (%)	Ethnicity / race, N (%)	Education years (SD)	Psychosocial risk factor(s) (Measure)[†]	Brain age tool modality
Leonardsen et al.(40), 2022	UKBB, UK	HC	8,066	Range 45-82[g]	NR	NR	NR	Worrier / anxious feelings (NR); loneliness, isolation (NR); neuroticism (NR)	sMRI
Lin et al. (51), 2021	Pitt-MDD MD2 ACC - Females, US	MDD	13	Range 5% 26.5– 95% 64.75	13 (100%)	NR	NR	MDD cases (Clinical records, toxicology results, and autopsy data)	Brain tissue in ACC and dlPFC (Brodmann area 47 and 11)
		HC	13		13 (100%)	NR	NR		
	Pitt-MDD MD2 DLPFC - Females, US	MDD	16	Range 5% 27.1– 95% 68.6	16 (100%)	NR	NR	MDD cases (Clinical records, toxicology results, and autopsy data)	
		HC	16		16 (100%)	NR	NR		
	Pitt-MDD MD2 DLPFC - Males, US	MDD	14	Range 5% 28.2– 95% 61.65	0 (0%)	NR	NR	MDD cases (Clinical records, toxicology results, and autopsy data)	
		HC	14		0 (0%)	NR	NR		
Luo et al. (55), 2022	REST-meta-MDD consortium[h], China	MDD	1,276	36.23 (14.62)∗	NR	Chinese, 1,276 (100%)	NR	MDD cases (ICD-10 or DSM-IV hospital diagnosis)	fMRI
		HC	1,101	36.25 (15.58)∗	NR	Chinese, 1,101 (100%)	NR		
Mareckova et al.(69), 2020	ELSPAC, Czech Republic	HC	131	23.84 (0.41)	70 (53.4%)	White, 131 (100%)	Elementary school (1.5%) High school (57.3%) Undergraduate degree (38.9%) Master's degree (2.3%)	General mood and anxiety (POMS and STAI)	sMRI
Moon et al. (20), 2025	HCP, US	HC	1,064	28.70 (3.70)	574 (53.9%)	NR	NR	Loneliness (NR); psychological stress (NR); neuroticism (NEO-FFI-60)	sMRI FA sMRI + FA

Continued on next page

Table 2
Summary of results

Author, year	Cohort, Country	Population	N	Age (SD)	Female, N (%)	Ethnicity / race, N (%)	Education years (SD)	Psychosocial risk factor(s) (Measure)†	Brain age tool modality
Xu et al. (42), 2025	GS:STRADL, UK	MDD	248	57.64 (9.22)	181 (73.0%)	NR	NR	MDD cases (SCID for DSM4)	sMRI
		HC	585	60.73 (9.55)	297 (50.8%)	NR	NR		
	UKBB, UK	MDD	3,717	61.52 (7.19)	2,527 (68%)	NR	NR	MDD cases (CIDI-SF)	
		HC	8,301	64.01 (7.33)	3,876 (46.7%)	NR	NR		
Zhao et al.(47), 2022	Veterans Affairs National PTSD Brain Bank, US	Total sample	94	42.49 (11.12)	39 (41.5%)	White, 73 (77.7%) Black, 21 (22.3%)	NR	MDD cases (next-of-kin informant MINI v6.0, Lieber Psychological Autopsy Interview); PTSD cases (next-of-kin informant MINI v6.0, post-mortem PTSD checklist for DSM-5, Lieber Psychological Autopsy Interview, psychiatrist confidence ratings in diagnosis ≥ 3)	Brain tissue in dlPFC, vmPFC and motor cortex
		MDD without PTSD	32	NR	NR	NR	NR		
		PTSD or MDD	70	NR	NR	NR	NR		
		PTSD and MDD	34	NR	NR	NR	NR		

Author, year	Cohort, Country	Population	N	Age (SD)	Female, N (%)	Ethnicity / race, N (%)	Education years (SD)	Psychosocial risk factor(s) (Measure)†	Brain age tool modality

† The psychosocial risk factors are measured by cases or controls, severity of symptoms within cases, severity of symptoms within cases plus controls or in a healthy control population. * Samples included participants under the age of 18.In the study by Han et al. (2021), the HC group age ranged 12–36 and MDD group 11–37. Luo et al. (2022) reported that the combined MDD and HC groups ranged from 12–82 years. Wolf et al. (2021) reported age at death ranged 17.35–92.25 years. Studies did not report number of participants under the age of 18. a N = 145 (missing data on education for 44 participants). b HC group is reported for the combined N = 219 for training the model and N = 218 for between-group comparison of BrainAGE with MDD chosen at random. c AFFDIS, CSAN, DCHS, FIDMAG, Hiroshima 1, Hiroshima 2, MOODS/DEP-ARREST CLIN, MOTAR, NESDA, Novosibirsk, Singapore, SoCAT, StanfFAA, TiPs cohoers.d Barcelona, BiDirect, CLiNG, Dublin, Edinburgh (Bipolar Family Study), FOR2107 – Marburg, FOR2107 – Münster, Houston, BRDECC London, McMaster University Mood Disorders, Melbourne, MPIP, Münster Neuroimaging Cohort, QTIM, Sao Paolo (Wellcome), SHIP/TREND, SHIP, Stanford, Sydney cohorts. e N = 300 (missing data on education for 35 participants). f N = 96 (missing data on education for 6 participants). g The age range is only provided for the 40,330 participants in the UKBB sample used for training (n = 34285), validating (n = 8544) and testing (n = 8066) the brain age tool. h National Clinical Research Center for Mental Disorders, Peking University, The Affiliated Guangji Hospital of Soochow University, The Second Xiangya Hospital of Central South University, Department of Psychiatry, Shanghai Jiao Tong University School of Medicin, Department of Psychiatry, Shanghai Jiao Tong University School of Medicine, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Department of Psychiatry, First Affiliated Hospital, China Medical University, The First Affiliated Hospital of Jinan University, First Hospital of Shanxi Medical University, Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University, Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University, The First Affiliated Hospital of Xi an Jiaotong University, Xian Central Hospital, The Second Xiangya Hospital of Central South University, Zhongda Hospital, School of Medicine, Southeast University, Huaxi MR Research Center, West China Hospital of Sichuan University, Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University, The First Affiliated Hospital, College of Medicine, Zhejiang University, Anhui Medical University, Faculty of Psychology, Southwest University, Beijing Anding Hospital, Capital Medical University, The Institute of Mental Health, Second Xiangya Hospital of Central South University, Mental Health Center, West China Hospital, Sichuan University, First Affiliated Hospital of Kunming Medical University, Department of Neurology, Affiliated ZhongDa Hospital of Southeast University. i N = 19 (missing data on education for 5 participants). Abbreviations: ACC, Anterior Cingulate Cortex; ALSPAC SCZ-RbG, Avon Longitudinal Study of Parents and Children Schizophrenia Recall by Genotype; ASPREE-NEURO, Aspirin in Reducing Events in the Elderly – Neuroimaging Sub-study; BAI, Beck Anxiety Inventory; BASE-II, Berlin Aging Study II; BDI, Beck Depression Inventory; CAN-BIND, Canadian Biomarker Integration Network in Depression; CAPS-4, Clinician-Administered PTSD scale for DSM-4; CAPS-5, Clinician-Administered PTSD scale for DSM-5; CARDIA, coronary artery risk development in young adults; CES-D, centre for epidemiological studies depression scale; CIDI, composite international diagnostic interview; CIDI-SF, composite international diagnostic interview – short form; COI, Centre of Innovation at Hiroshima University; DMHDS, Dunedin Multidisciplinary Health and Development Study; dlPFC, dorsolateral prefrontal cortex; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; DTS, Davidson Trauma Scale; EEG, electroencephalogram; ELSPAC, European Longitudinal Study of Pregnancy and Childhood; EMBARC, Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care; ENIGMA MDD, Enhancing Neuroimaging Genetics Through Meta-Analysis Major Depressive Disorder; ENIGMA-PGC, Enhancing Neuro Imaging Genetics Through Meta-Analysis–Psychiatric Genomics Consortium; EPQ-R-S, Eysenck Personality Questionnaire-Revised Short Form; FA, fractional anisotropy; FACHS, Family and Community Health Study; FINA, Functional Neuroanatomy Correlates of Worry in Older Adults; fMRI, functional magnetic resonance imaging; GAD, Generalised Anxiety Disorder; GDS, Geriatric Depression Scale; GS:STRADL, Generation Scotland: Stratifying Resilience and Depression Longitudinally Follow-Up Study; HARS, Hamilton Anxiety Rating Scale; HC, healthy controls; HCP, Human Connectome Project; HDRS, Hamilton Rating Scale for Depression; HKH, Hiroshima Kajikawa Hospital; HRC, Hiroshima Rehabilitation Centre; HUH, Hiroshima University Hospital; ICD-10, International Classification of Diseases, Tenth Revision; IDS, Inventory for Depressive Symptoms; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, Major Depressive Disorder; MINI, Mini International Neuropsychiatric Interview; mini-MASQ, The Mini Mood and Anxiety Symptom Questionnaire; MODECT, Mood Disorders in Elderly Treated with Electroconvulsive Therapy; N, number of people; NEO-FFI, Neuroticism Subscale from 5-Factor Inventory; NESDA, Netherlands Study of Depression and Anxiety; NKI-Rockland, Enhanced Nathan Kline Institute Rockland County; NR, not reported; NVQ, National Vocational Qualification; PCL-5, Post-Traumatic Stress Disorder Checklist for DSM-5; PCL-C, Post-Traumatic Stress Disorder Checklist Civilian Version; PCL-M, Post-Traumatic Stress Disorder Checklist Military Version; PHQ, Patient Health Questionnaire; POMS, Profile of Mood States Questionnaire; PSS, Perceived Stress Scale; PTSD, Post-Traumatic Stress Disorder; QIDS-SR, Quick Inventory of Depressive Symptomatology–Self-Report; RCS, Rutter Child Scale; REMBRANDT, Recurrence Markers, Cognitive Burden, and Neurobiological Homeostasis in Late-Life Depression; SAFE, Syncope and Falls in the Elderly; sMFQ, Short Mood and Feeling Questionnaire; sMRI, Structural Magnetic Resonance Imaging; SCID, Structured Clinical Interview for DSM Disorders; STAI, Spielberger State-Trait Anxiety Inventory; TANMIND, Taiwan Aging and Mental Illness Neuroimaging; TWH, Toronto Western Hospital; UK, United Kingdom; UKBB, United Kingdom Biobank; US, United States; UTO, University of Tokyo; vmPFC, ventromedial prefrontal cortex; WCM, Weill Cornell Medicine; WTC-HP GRC, World Trade Centre Health Program General Responder Cohort.

Several studies used overlapping cohorts. Two studies examined depression in the CAN-BIND cohort.(37,38) Four studies reported on different risk factors from the United Kingdom Biobank.(39–42) Two studies examined depression in the ENIGMA major depressive disorder (MDD) working group.(43,44), and the Ludwig-Maximilians University cohort.(21,45) The Veterans Affairs National PTSD Brain Bank was used in two studies to investigate depression and PTSD.(46,47)

3.3 Quality Appraisal

Quality of cross-sectional studies varied (Table 2. **Supplementary table 5A-B** contains the full ratings). Risk of bias varied in studies of MDD cases (8 low, 11 moderate, 6 high), depressive symptoms (7 low, 7 moderate, 2 high) and anxiety symptoms (1 low, 3 moderate, 1 high), psychological stress (1 low, 1 moderate, 2 high), loneliness (1 moderate, 2 high), and neuroticism (1 low, 2 moderate, 1 high). The one study of anxiety cases had a low risk of bias and the one study in social isolation had a moderate risk of bias. Most PTSD studies had moderate risk (Cases: 1 low, 3 moderate; symptoms: 1 moderate).

Longitudinal studies were consistently good quality; all studies of depressive symptoms and loneliness had low risk of bias.

3.3 Participant characteristics

Across 44 studies, sample age spanned early-adulthood (*k* = 15, 34.1%), middle-adulthood (*k* = 19, 43.2%) and older-adulthood (*k* = 6, 13.6%), with four studies reporting broad ranges. Proportion of female participants ranged from 0% to 100% (median: 53.66%), with two studies not reporting this. Ethnicity/race was not reported by 26 studies (59.1%); among those that did, white ethnicity predominated, ranging from 43.8% to 100% (*k* = 12, median: 79.35%).

3.4 Psychosocial measures

Many studies assessed multiple psychosocial risk factors. Depression was most frequently assessed ([*k* = 36, 81.8%]; MDD cases: 18, symptoms: 11, both: 7). Followed by anxiety ([*k* = 5, 11.4%]; symptoms: 4, cases and symptoms: 1), PTSD ([*k* = 4, 9.1%]; cases: 3, cases and symptoms: 1), psychological stress (*k* = 4 [9.1%]), social isolation (*k* = 2 [4.5%]), loneliness (*k* = 4 [9.1%]), and neuroticism (*k* = 4 [9.1%]). No studies assessed psychological trauma. **Supplementary table 6** contains an overview of measures.

3.5 Brain age tools

Table 3 summarises the brain age tools used. Across 44 studies, 29 independent tools were used. Three studies used multiple tools, and seven applied one tool in multiple ways (e.g., input features, brain region).(20,41,46–51) The most common modality was sMRI (*k* = 37, 84.1%); followed by post-mortem brain tissue (*k* = 6, 13.6%), fMRI (*k* = 2, 4.5%), FA (*k* = 1, 2.3%), multimodal sMRI + FA (*k* = 1, 2.3%), EEG (*k* = 1, 2.3%) or whole blood (*k* = 1, 2.3%). The most used sMRI tool was developed by Cole (*k* = 7, 33.3%), followed by the ENIGMA MDD working group (*k* = 5, 23.8%).(44,52) Across other modalities, no tool was used more than once.

Table 3
Overview of brain age tools included.

Author, year	Study Design	Unadjusted association(s)			Adjusted association(s)†				Risk of bias rating
		Statistical test	N	Summary of results	Statistical test	Covariates for primary model	N	Summary of results	
Leonardsen et al.(40), 2022	Cross-sectional	-	-	-	Linear regression	Age, sex	8,066	No association with brain age delta (β = 0.04, p= .258)	High
Moon et al. (20), 2025	Cross-sectional	Spearman's rank correlation	1,061	No association with sMRI + FA brain predicted age (r = − .035, p= .258, FDR corr p= .429)	-	-	-	-	Moderate
		-	-	-	General linear model	Age, sex, handedness, and education	1,061	No association with sMRI brain age gap (t= -1.941, r = − .060, FDR corr p= .263)	
								No association with FA brain age gap (t= -1.427, r = − .044, FDR corr p= .543)	
								No association with sMRI + FA brain age gap (t= -1.655, r = − .051, FDR corr p= .310)	

Note: All summary findings are reported as presented in the original studies.

† Where multiple models were reported, the primary model was chosen. * Estimate should be used with caution as the models used interaction terms.

Abbreviations: ACC, Anterior Cingulate Cortex; Adj, Adjusted; ANCOVA, Analysis of Covariance; ANBA, Amyloid Negative Brain Age; ARMS, At Risk Mental State for Psychosis; BA11, Brodmann Area 11; BA47, Brodmann Area 47; BAG, Brain Age Gap; BAI, Beck Anxiety Inventory; BDI, Beck depression inventory; BDI–II, Beck Depression Inventory Second Edition; BDNFm, Brain–derived Neurotrophic Factor Methylation; BMI, Body Mass Index; BPD, Borderline Personality Disorder; BrainAGE, Brain Age Gap Estimate; BrainAGE–diff, Brain Age Gap Estimate Difference; Brain–PAD, Brain Predicted Age Difference; BSAGE, Brain Structure Age Gap Estimate; CC–Bd, Cortical Clock–Blood Based; CES–D, Centre for Epidemiological Studies Depression Scale; Corr, Corrected; deepBA, Deep Brain Age; dlPFC, Dorsolateral Prefrontal Cortex; DNAm, Deoxyribonucleic Acid Methylation; EphysAGE, Electrophysiological Age Gap Estimation; FA, Fractional Anisotropy; FDR, False Discovery Rate; FEW, Family Wise Error; GDS, Geriatric Depression Scale; G–brainAGE, Global Brain Age Gap Estimate; GS:STRADL, Generation Scotland: Stratifying Resilience and Depression Longitudinally Follow–up Study; HC, Healthy Controls; HDRS, Hamilton Rating Scale for Depression; HDRS–17, Hamilton Rating Scale for Depression – 17 Item; IDS, Inventory for Depressive Symptoms; L–brainAGE, Local Brain Age Gap Estimate; MDD, Major Depressive Disorder; MMSE, Mini Mental State Exam; N, Number of People; NR, Not Reported; PC1, Principle Component 1; PC2, Principle Component 2; PC3, Principle Component 3; PTSD, Post–Traumatic Stress Disorder; qSV1, Quality Surrogate Variable 1; qSV2, Quality Surrogate Variable 2; qSV3, Quality Surrogate Variable 3; RNA, Ribonucleic Acid; SZ, Schizophrenia; SES, Socioeconomic Status; sMRI, Structural Magnetic Resonance Imaging; SWLS, Satisfaction With Life Scale; TICV, Total Intracranial Volume; TWA, Time Weighted Average; UKBB, United Kingdom Biobank; vmPFC, Ventromedial Prefrontal Cortex; WTC, World Trade Centre.

Author, year	Brain age toolY (metric)	Training sample				Model	
		Origin	Sample size	Age (SD)	Females N (%)	Input Features	Algorithm
Brain age modality: sMRI							
Abram et al. (72), 2023	Han et al. (44) (BrainAGE-diff†)	ENIGMA MDD working group	2,188	40.9 (15.6)	1236 (56.5%)	77 structural brain metrics including cortical thickness, cortical surface area, subcortical volumes	Ridge regression
Ballester et al. (37), 2023	Kaufmann et al.(88) (BAG†)	ABIDE, ABM, ADDNEUROMED, ADHD200, ADHDWUE, ADNI1, ADNI2, BETULA, CAMCAN, CIMH, CORR, DLBS, DS000030, DS000119, DS000171, DS000202, DS000222, HCP, HUBIN, HUNT, IXI, KASP, MALTOSLO, NCNG, NIMAGE, NORCOG, OASIS, PING, PNC, SALD, SCHIZCONNECT1, SCHIZCONNECT2, SCORE, SLIM, STROKEMRI, TOP, UBA, UKBB, UNIBA	35,474	Range 3–89	18990 (53.5%)	1118 structural features including 360 cortical thickness, 360 cortical area, 360 cortical volume and 38 cerebellar–subcortical and cortical summary statistics	Gradient Tree boosting
Ballester et al. (38), 2021	Clausen et al.(52)[a] (Brain-PAD†)	AIBL, DLBS, GSP, IXI, NKI-Rockland, OASIS-1, SALD	3,377	40.6 (21.4)	NR	Grey matter, white matter and CSF	Gaussian Processes Regression
Besteher et al. (58), 2019	Franke et al. (89) (BrainAGE†)	IXI	743	43.9 (NR)	427 (57.5%)	Grey matter voxels	Relevance vector regression
Christman et al.(60), 2020	Bermudez et al.(90) (BAG†)	ABIDE, ADHD-200, BLSA, Cutting, FCON-1000, IXI, NDAR, NKI-Rockland, OASIS	5,048	29.1 (22.7)	2,401 (47.6%)	Volume of 132 distinct regions	Deep convolutional neural network regression
Clausen et al. (52), 2022	Clausen et al. (52)[a] (Brain-PAD†)	AIBL, DLBS, GSP, IXI, NKI-Rockland, OASIS-1, SALD	3,377	40.6 (21.4)	NR	Grey matter, white matter and CSF	Gaussian Processes Regression
Author, year	**Brain age toolY (metric)**	**Training sample**				**Model**	
		Origin	**Sample size**	**Age (SD)**	**Females N (%)**	**Input Features**	**Algorithm**
Constantinides et al.(48), 2024	Han et al. (44) (Brain-PAD†)	ENIGMA MDD working group	2,188	40.87 (15.6)	1236 (56.5%)	77 structural brain metrics including 7 subcortical volumes, 34 cortical thickness and 34 surface area, lateral ventricles and total intracranial volume measures	Ridge regression

Author, year	Brain age toolY (metric)	Training sample				Model	
		Origin	Sample size	Age (SD)	Females N (%)	Input Features	Algorithm
Brain age modality: sMRI							
	Yu et al.(91) (Brain-PAD†)	ABCD, ABIDE, ABIDE II, ADHD200, AMC, Ann Arbor a, Ann Arbor b, Atlanta, Baltimore, Bangor, Barcelona 3T, Beijing_Zang, Berlin_Margulies, Betula, BIG, BIL&GIN, Bonn, BrainSCALE, BRCATLAS, Cambridge, Cam-CAN, Cardiff, CLiNG, CODE, COMPULS/TS EUROTRAIN, GSP, HCP Adult Brain, HCP Aging, HCP Development, Healthy Brain Network/CMI, ICBM, IMAGEN, IMH, Indiana, IRCCS-FSL, Leiden, Leiden_2180, Leiden_2200, MAS, MCIC, Melbourne, Milwaukee_b, Muenster, Munchen, Neuroventure, Newark, NewYork_b, NUIG, NYU_TRT, Olin, Orangeburg, Oulu, Oxford, PaloAlto, PING, QTIM, Queensland, Rockland, Saint-Louis, Sydney, UKBB, UNIBA, UPENN, UTH	35,683	Range 5–90	19123 (53.6%)	150 morphometric features including 68 of cortical thickness, 68 of cortical surface area and 14 regional subcortical volumes	Support Vector Regression with Radial Basis Function
Dai et al.(56), 2025	Dai et al. (56) (Brain-PAD†, predicted brain age)	COI, HUH, HRC, HKH, UTO	219	NR	NR	372 regions of interest including 358 for cortical thickness and 14 for subcortical volume	Support Vector Regression

Author, year	Brain age toolY (metric)	Training sample				Model	
		Origin	Sample size	Age (SD)	Females N (%)	Input Features	Algorithm
De Lange et al. (39), 2021	Kaufmann et al.(88) (BAG†)	ABIDE, ABM, ADDNEUROMED, ADHD200, ADHDWUE, ADNI1, ADNI2, BETULA, CAMCAN, CIMH, CORR, DLBS, DS000030, DS000119, DS000171, DS000202, DS000222, HCP, HUBIN, HUNT, IXI, KASP, MALTOSLO, NCNG, NIMAGE, NORCOG, OASIS, PING, PNC, SALD, SCHIZCONNECT1, SCHIZCONNECT2, SCORE, SLIM, STROKEMRI, TOP, UBA, UKBB, UNIBA	35,474	Range 3–89	18,990 (53.5%)	1118 structural features including 360 cortical thickness, 360 cortical area, 360 cortical volume and 38 cerebellar–subcortical and cortical summary statistics	Gradient Tree boosting
Dintica et al. (67), 2023	Habes et al. (92) (Predicted brain age)	iSTAGING consortium including data from ADNI 1, ADNI 2, Penn-ABC, Penn-PMC, SHIP, UKBB, BLSA, AIBL, CARDIA, ACS, BIOCARD, WRAP	8,284	60.5 (13.1)	4,515 (54.5%)	69 grey matter, white matter regions and ventricular volumes	Support vector regression
Franke et al. (63), 2013	Franke et al. (89) (BrainAGE†)	IXI	561	48.6 (16.5)	311 (55.4%)	Grey matter voxels	Relevance vector regression
Han et al.(43), 2022	Han et al. (44) (Brain-PAD†)	ENIGMA MDD working group	2,188	40.9 (15.6)	1,236 (56.5%)	77 structural brain metrics including 7 subcortical volumes, 34 cortical thickness and 34 surface area, lateral ventricles and total intracranial volume measures	Ridge regression
Han et al. (44), 2021	Han et al. (44) (Brain-PAD†)	ENIGMA MDD working group	2,188	40.9 (15.6)	1,236 (56.5%)	77 structural brain metrics including 7 subcortical volumes, 34 cortical thickness and 34 surface area, lateral ventricles and total intracranial volume measures	Ridge regression

Author, year	Brain age toolY (metric)	Training sample				Model	
		Origin	Sample size	Age (SD)	Females N (%)	Input Features	Algorithm
Han et al. (54), 2021	Han et al. (44) (Brain-PAD†)	ENIGMA MDD working group	2,188	40.9 (15.6)	1,236 (56.5%)	77 structural brain metrics including 7 subcortical volumes, 34 cortical thickness and 34 surface area, lateral ventricles and total intracranial volume measures	Ridge regression
Han et al. (53), 2021	Han et al. (53) (Brain-PAD†)	Affiliated Hospital of Zhengzhou University, SALD	400	28.2 (10.0)	157 (39.3%)	268 regions of grey matter volume	Gaussian process regression
Jawinski et al.(50), 2022	Jawinski et al. (50) (BAG†)	UKBB	32,634	Range 45–82	NR	Grey matter segmentations	Relevance Vector Machine, Gradient Tree boosting and Gradient linear boosting stacked by linear regression
						White matter segmentations	
						500 grey matter and white matter segmentations	
Jha et al. (61), 2023	Clausen et al. (52)[a] (BAG†)	AIBL, DLBS, GSP, IXI, NKI-Rockland, OASIS-1, SALD	3,377	40.6 (21.4)	NR	Grey matter, white matter and CSF	Gaussian processes regression
Karim et al.(49), 2025	Ly et al.(93) (Brain age residual)	ADNI, IXI, OASIS-3	757	55.4 (17.5)	419 (55.4%)	Whole brain and voxel wise grey matter densities	Gaussian processes regression
	Bermudez et al.(90) (Brain age residual)	ABIDE, ADHD-200, BLSA, Cutting, FCON-1000, IXI, NDAR, NKI-Rockland, OASIS	5,048	29.1 (22.7)	2,401 (47.6%)	Volume of 132 distinct regions	Deep convolutional neural network regression
Karim et al.(62), 2021	Ly et al.(93) (Predicted brain age)	ADNI, IXI, OASIS-3	757	55.4 (17.5)	419 (55.4%)	Whole brain and voxel wise grey matter densities	Gaussian processes regression

Author, year	Brain age toolY (metric)	Training sample				Model	
		Origin	Sample size	Age (SD)	Females N (%)	Input Features	Algorithm
Koutsouleris et al.(45), 2014	Koutsouleris et al.(45) (BrainAGE†)	Munich database: Department of Psychiatry and Psychotherapy, Ludwig-Maximilian University, IXI, OASIS	800	38.2 (14.2)	NR	Grey matter volumes including subcortical and periventricular, orbitofrontal, cerebellar, limbic, and perisylvian regions, affine grey matter including cingulate, orbitofrontal, perisylvian, subcortical, and (para) limbic structures	Support Vector Regression
Kuo et al. (59), 2020	Kuo et al.(59) (Brain-age gap†)	ILAS, TANMIND	800	62.3 (8.7)	429 (53.6%)	40 grey matter large-scale structural covariance networks including the caudate nucleus, putamen, hippocampus, amygdala, and cerebellar regions	Least absolute shrinkage and selection operator regression
Lay-Yee et al. (73), 2023	Liem et al. (94) (BrainAGE†)	LIFE	2,354	58.68 (15.2)	1,120 (47.6%)	Multiple measures of brain structure – i.e. cortical thickness, surface area, and volumes of subcortical gray matter, white matter, and cerebrospinal fluid	Support Vector Regression
Leonardsen et al.(40), 2022	Leonardsen et al.(40) (brain age delta†)	HBN, ADHD200, PING, ds000119, ABIDE, SLIM, ABIDE2, Beijing, AOMIC, CoRR, MPI-Lemon, HCP, FCON1000, NKI Rockland, SALD, ds000222, DLBS, CamCAN, UKB, OASIS3, ds000202	53,542	Range 3–95	27,715 (51.8%)	Learnt representations from a simple Fully Convolutional Network with a SoftMax output	Simple Fully Convolutional Network
Mareckova et al.(69), 2020	Pardoe & Kuzniecky. (95) (BAG†)	ABIDE, ABIDE II, CoRR, DLBS, NKI-Rockland	2,367	Range 6–89	NR	5124 features from cortical thickness maps	Relevance vector machine regression and Gaussian processes
Moon et al. (20), 2025	Moon et al. (20) (Brain age gap†)	HCP, Cam-CAN	1,703	38.38 (17.14)	896 (52.6%)	Global context from the sMRI images	Global-Local Attention (GLA) Transformer
Rilling et al. (70), 2025	Kalc et al. (96) (BrainAGE†)	IXI, OASIS-3, Cam-CAN, SALD, NKI-Rockland	1,894	50.1 (13.5)	1,127 (59.5%)	Grey matter, white matter, and cerebrospinal fluid volumes	Gaussian process regression

Author, year	Brain age toolY (metric)	Training sample				Model	
		Origin	Sample size	Age (SD)	Females N (%)	Input Features	Algorithm
Sanford et al. (41), 2025	Yu et al. (91) (G-brainAGE†)	ABCD, ABIDE, ABIDE II, ADHD200, AMC, Ann Arbor a, Ann Arbor b, Atlanta, Baltimore, Bangor, Barcelona 3T, Beijing_Zang, Berlin_Margulies, Betula, BIG, BIL&GIN, Bonn, BrainSCALE, BRCATLAS, Cambridge, Cam-CAN, Cardiff, CLiNG, CODE, COMPULS/TS EUROTRAIN, GSP, HCP Adult Brain, HCP Aging, HCP Development, Healthy Brain Network/CMI, ICBM, IMAGEN, IMH, Indiana, IRCCS-FSL, Leiden, Leiden_2180, Leiden_2200, MAS, MCIC, Melbourne, Milwaukee_b, Muenster, Munchen, Neuroventure, Newark, NewYork_b, NUIG, NYU_TRT, Olin, Orangeburg, Oulu, Oxford, PaloAlto, PING, QTIM, Queensland, Rockland, Saint-Louis, Sydney, UKBB, UNIBA, UPENN, UTH	35,683	Range 5–90	19,123 (53.6%)	150 regional measures of cortical thickness (n = 68) and surface area (n = 68) and subcortical volume (n = 14)	Support Vector Regression with Radial Basis Function
	Popescu et al.(97) (L-brainAGE†)	DLBS, Cam-CAN, SALD, Wayne State and BAHC comprising ABIDE, Beijing Normal University, Berlin School of Brain Mind, CADDementia, Cleveland Clinic, ICBM, IXI, MCIC, MIRIAD, NEO2012, NKI-Rockland, OASIS, WUS and TRAIN-39.	3,764	43.9 (15.8)	1,897 (50.4%)	Grey and white matter segments including in the prefrontal cortex and periventricular areas	Convolutional Neural Network
Seeley et al. (71), 2025	Nguyen et al.(98) (BSAGE†)	ABIDE I, ADNI, AIBL, ICBM, C-MIND, IXI, NDAR, OASIS1	2,887	38.0 (26.5)	1,386 (48.0%)	133 brain structure regions	Support vector regression

Author, year	Brain age toolY (metric)	Training sample				Model	
		Origin	Sample size	Age (SD)	Females N (%)	Input Features	Algorithm
Sone et al.(65), 2022	Beheshti et al.(99) (Brain-PAD†)	IXI, OASIS, ADNI, PPMI	839	63.6 (13.4)	463 (55.2%)	3747 grey or white matter intensity features	Support vector regression
Wagenmakers et al.(64,65), 2023	Clausen et al. (52)[a] (BrainAGE†)	AIBL, DLBS, GSP, IXI, NKI-Rockland, OASIS-1, SALD	3,377	40.6 (21.4)	NR	Grey matter, white matter and CSF	Gaussian processes regression
Wrigglesworth et al.(66), 2022	Clausen et al. (52)[a] (Brain-PAD†)	AIBL, DLBS, GSP, IXI, NKI-Rockland, OASIS-1, SALD	3,377	40.6 (21.4)	NR	Grey matter, white matter and CSF	Gaussian processes regression
Xu et al.(42), 2025	Clausen et al. (52)[a] (Brain-PAD†)	AIBL, DLBS, GSP, IXI, NKI-Rockland, OASIS-1, SALD	3,377	40.6 (21.4)	NR	Grey matter, white matter and CSF	Gaussian processes regression
Brain age modality: fMRI							
Dunlop et al. (19), 2021	Dunlop et al. (19) (Brain-PAD†)	NKI-Rockland, WCM, TWH	710	Range 18 to 89	NR	600 resting-state features, predominantly of the decreased intra-network, especially the sensorimotor, visual, auditory, salience, and cingulo-opercular task control networks	Support vector regression
Luo et al.(55), 2022	Luo et al.(55) (Brain-PAD†)	REST-meta-MDD consortium [b]	1,101	NR	NR	20 functional connectivity features including cerebellum, superior and vermis, the medial superior frontal gyrus and middle temporal gyrus, the amygdala and lenticular nucleus putamen	Stacking model

Author, year	Brain age toolY (metric)	Training sample				Model	
		Origin	Sample size	Age (SD)	Females N (%)	Input Features	Algorithm
Brain age modality: FA							
Moon et al.(20), 2025	Moon et al.(20) (brain age gap†)	HCP, Cam-CAN	1,703	38.38 (17.14)	896 (52.6%)	Local features from patches of the FA metric	Global-Local Attention (GLA) Transformer
Brain age modality: multimodal sMRI + FA							
Moon et al. (20), 2025	Moon et al.(20) (Brain predicted age, brain age gap†)	HCP, Cam-CAN	1,703	38.38 (17.14)	896 (52.6%)	Local features from patches of the FA metric images and global context from the sMRI images	Global-Local Attention (GLA) Transformer
Brain age modality: EEG							
Sarisik et al. (21), 2024	Sarisik et al.(21) (EphysAGE†)	Ludwig-Maximilians University	245	47.0 (4.5)	119 (48.7%)	1501 features including 1330 power spectrum density features and 171 connectivity features	Support vector regression
Brain age modality: whole blood							
Simons et al. (68), 2023	Shireby et al. (100) (CC-Bd†)	Edinburgh, Harvard, Lieber Institute, LBB2, Maudsley, Montreal, Mount Sinai, NICHD, Oxford, ROSMAPmo	1,047	56.5 (24.6)	362 (34.6%)	347 DNA methylation sites	Elastic net regression
Brain age modality: brain tissue							
Han et al.(57), 2018	Han et al.(57) (DNAmAge residuals)	NESDA	1,130	41.5 (13.0)	729 (64.5%)	100,000 CpG sites	Elastic net regression with parameter alpha was set to zero (i.e. ridge regression)
Lin et al. (51), 2021	Lin et al.(51) (Delta age†)	Allegheny County Coroner's Office, Pittsburgh human postmortem cohort	204	50.3 (14.7)	38 (18.6%)	68 genes in BA47 76 genes in BA11	Elastic net regression with leave-one-out-cross-validation

Author, year	Brain age toolY (metric)	Training sample				Model	
		Origin	Sample size	Age (SD)	Females N (%)	Input Features	Algorithm
Brain age modality: brain tissue							
Wolf et al. (46), 2021	Horvath(23) (DNAm age residuals)	82 illumina DNA methylation array datasets	7,844	Range 0-100	NR	335 CpGs	Elastic net regression
Zhao et al. (47), 2022	Ren & Kuan(24) (RNA age residuals)	GTEx V6	9,446	NR	NR	472 genes	Elastic net regression

† All brain age metrics refer to a conceptually equivalent brain age gap metric.

Y The citation is the published paper detailing the development and validation of the brain age estimation tool. These papers were referred to when the included articles did not detail the extracted data. a There is no specific journal article associated with the brainageR tool developed by Cole, see the cited paper for further details on the model. b National Clinical Research Center for Mental Disorders, Peking University, The Affiliated Guangji Hospital of Soochow University, The Second Xiangya Hospital of Central South University, Department of Psychiatry, Shanghai Jiao Tong University School of Medicin, Department of Psychiatry, Shanghai Jiao Tong University School of Medicine, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Department of Psychiatry, First Affiliated Hospital, China Medical University, The First Affiliated Hospital of Jinan University, First Hospital of Shanxi Medical University, Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University, Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University, The First Affiliated Hospital of Xi an Jiaotong University, Xian Central Hospital, The Second Xiangya Hospital of Central South University, Zhongda Hospital, School of Medicine, Southeast University, Huaxi MR Research Center, West China Hospital of Sichuan University, Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University, The First Affiliated Hospital, College of Medicine, Zhejiang University, Anhui Medical University, Faculty of Psychology, Southwest University, Beijing Anding Hospital, Capital Medical University, The Institute of Mental Health, Second Xiangya Hospital of Central South University, Mental Health Center, West China Hospital, Sichuan University, First Affiliated Hospital of Kunming Medical University, Department of Neurology, Affiliated ZhongDa Hospital of Southeast University. Abbreviations: ABCD Healthy, The Adolescent Brain Cognitive Development Study; ABIDE, the Autism Brain Imaging Data Exchange; ACS, The Adult Children Study at Washington University; ADHD200, Attention Deficit Hyperactivity Disorder – ADHD200 sample; AIBL, Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing; AMC, Amsterdam Medisch Centrum; BA11, Brodmann Area 11; BA47, Brodmann Area 47; BAG, Brain Age Gap; BAHC, brain age healthy control dataset; BBRCATLAS, Biomedical Research Centre Atlas; BLSA, Baltimore Longitudinal Study of Aging; BIG, Brain Imaging Genetics; BIL&GIN, Brain Imaging of Lateralization by the Groupe d'Imagerie Neurofonctionnelle; BIOCARD, The Biomarkers of Cognitive Decline Among Normal Individuals in the Johns Hopkins University; Brain−PAD, Brain Predicted Age Difference; BrainAGE, Brain Age Gap Estimate; BrainAGE−diff, Brain Age Gap Estimate Difference; BrainSCALE, Brain Structure and Cognition: an adolescence longitudinal twin study; BSAGE, Brain Structure Age Gap Estimate; Cam−CAN, Cambridge Centre for Aging and Neuroscience; CARDIA, The Coronary Artery Risk Development in Young Adults; CC−Bd, Cortical Clock−Blood Based; CLiNG, Clinical Neuroscience Göttingen; COI, Center of Innovation at Hiroshima university; CpG, Cytosine−phosphate−Guanine; CSF, Cerebrospinal Fluid; DLBS, Dallas Lifespan Brain Study; DNA, Deoxyribonucleic Acid; DNAm, Deoxyribonucleic Acid Methylation; DNAmAge, Deoxyribonucleic Acid Methylation Age Gap Estimate; EEG, Electroencephalogram; EphysAGE, Electrophysiological Age Gap Estimation; FCON−1000, 1000 Functional Connectomes Project; fMRI, Functional Magnetic Resonance Imaging; G−brainAGE, Global Brain Age Gap Estimate; GSP, Genome Superstruct Project; GTEx V6, Genotype−Tissue Expression Program version 6 release; HCP, human connectome project; HKH, Hiroshima Kajikawa Hospital; HRC, Hiroshima Rehabilitation Center; HUH, Hiroshima university hospital; ICBM, International Consortium for Brain Mapping; ILAS, I−LAN Longitudinal Aging Study; IMH, Institute of Mental Health, Singapore; iSTAGING, Imaging−based coordinate system for aging and neurodegenerative diseases; IXI, Information eXtraction from Images; L−brainAGE, Local Brain Age Gap Estimate; LIFE, Leipzig Research Centre for Civilization Diseases; MAS, Memory and Ageing Study; NDAR, National Database for Autism Research; NESDA – Netherlands Study of Anxiety and Depression; NICHD, National Institute of Child Health and Human Development; NKI−Rockland, Nathan Kline Institute Rockland Sample Enhanced; NR, Not reported; NUIG, National University of Ireland; NYU_TRT, New York University – Test−Retest Reliability; OASIS−1, Open Access Series of Imaging Studies−1; PING, Pediatric Imaging, Neurocognition, and Genetics; Penn−PMC, The University of Pennsylvania Memory Center cohort; QTIM, Queensland Twin Imaging Study; RNA, Ribonucleic Acid; ROSMAP, Religious Orders Study and Rush Memory and Aging Project; SALD, Southwest University Adult Lifespan Dataset; SHIP, The Study of Health in Pomerania; sMRI, Structural Magnetic Resonance Imaging; TANMIND, Taiwan Aging and Mental Illness Neuroimaging; TWH, Toronto Western Hospital; UKBB, United Kingdom Biobank; UNIBA, University of Bari Aldo Moro; UPENN, University of Pennsylvania; UTH, University of Texas Health; UTO, University of Tokyo; WCM, Weill Cornell Medicine; WRAP, Wisconsin Registry for Alzheimer's Prevention

Supplementary table 7 summarises brain age metrics used. Across and within psychosocial risk factors, no consistent pattern of associations emerged by brain age model or modality. Therefore, for simplicity, the terms 'brain age gap' (BAG), brain age residual (e.g. RNA residual) or brain age (when no difference between chronological age was estimated) were used to summarise findings; however detailed study metrics are shown in Table 3.

3.6 Narrative synthesis

3.6.1. Depression

3.6.1.1 MDD cases

Twenty-five studies examined cross-sectional associations. Half reported higher BAG in MDD versus controls (*k* = 13, 52%) and half reported no difference (*k* = 12, 48%). No longitudinal studies were identified.

In early-adulthood, five of eight studies reported higher brain age metrics in MDD versus controls. Using sMRI, three studies reported a 0.99-year, 0.59-year and 2.78-year higher BAG (43,53,54), and Koutsouleris et al.(45) found increased BAG. An fMRI study reported 4.43-years higher BAG.(55) Three sMRI studies reported no group differences in BAG.(37,38,54)

In middle-adulthood, eight of twelve studies reported higher brain age metrics in MDD compared with controls. Five sMRI studies reported higher predicted brain age or BAG in MDD (range: 0.05 to 1.08 years), with one finding higher BAG in the right insula and in the anterior cingulate extending to several medial and subcallosal frontal regions.(41,42,44,56) One fMRI study reported 2.11-years higher BAG.(19) Using post-mortem brain tissue, Han et al.(57) observed an 1.11-year higher epigenetic BAG. Using a post-mortem brain tissue and a transcriptomic approach, Zhao et al.(47) found that having MDD predicted RNA age residuals in the ventromedial prefrontal cortex (vmPFC). Two studies reported no differences in BAG using sMRI.(58,59) An EEG study found no difference in BAG, and a study using post-mortem brain tissue reported no difference with DNAm age residuals using an epigenetic approach.(21,46)

In older-adulthood, two studies, both using sMRI reported mixed findings. One reported no difference in brain age residuals using two brain age tools, while the other observed a higher BAG.(49,60) One article comprising three studies spanning early-to-older adulthood used post-mortem brain tissue and a transcriptomic approach, reporting no differences in BAG.(51)

3.6.1.2 Depressive symptoms

Cross-sectional

Seventeen studies investigated cross-sectional associations, four reported a positive association (23.5%) and thirteen (76.5%) reported no association. Associations varied by sample (MDD, healthy controls, combined) and age group. In MDD, the majority reported no association (k = 7, 87.5%), with one reporting an association (k = 1, 12.5%). This pattern was observed in healthy controls, with most reporting no association (k = 4, 80%), and one an association (k = 1, 20%). In combined samples, half reported no association (k = 2, 50%) and half an association (k = 2, 50%).

Six studies assessed early-adulthood, all using sMRI. In MDD, none of the four studies found an association between depressive symptoms (assessed using versions of the Hamilton Depression Rating Scale [HDRS]) and BAG.(43,45,53,61) In healthy controls, one study reported no association with BAG using two brain age tools.(48) In a combined MDD and healthy control sample, Han et al.(43) reported 0.04-year increase in BAG per symptom on the Beck Depression Inventory (BDI), though no association was seen with the HDRS; and Han et al.(54) observed a 0.07-year increase per symptom on the Inventory for Depressive Symptomology. In middle-adulthood, in MDD, two studies found no association with BAG using sMRI.(44,59) While one reported a 0.79-year higher BAG per 1-point increase on the HDRS, using fMRI.(19) One sMRI study found no link when using a combined sample.(62) In two sMRI studies of healthy controls, one reported no association with BAG and the other 5.4-years higher BAG.(39,63) In older-adulthood, four studies used sMRI and reported no association with BAG in MDD, healthy control, and combined samples.(50,64–66)

Longitudinal

Three studies reported mixed findings (positive association: k = 1; no association: k = 1; negative association: k = 1).

In early-adulthood, a study using sMRI reported a 1.14-year increase per 5-point increase over 25 years.(67) If scores increased by 16 or more, brain age increased by 2.75-years. In middle-adulthood, a study using an epigenetic cortical clock found that symptoms did not predict accelerated BAG over 11 years.(68) In older-adulthood, Wrigglesworth et al.(66) reported a slower rate of BAG using sMRI over three years with increased symptoms.

3.6.2. Anxiety

3.6.2.1 Anxiety cases

A cross-sectional sMRI study in early-adulthood reported 2.91-years higher BAG in individuals with an anxiety disorder compared with controls.(54) No longitudinal studies were identified.

3.6.2.2 Anxiety symptoms

Five cross-sectional studies all used sMRI; one reported a quadratic association, one a positive association, and three no association with either brain age or BAG. No studies used a longitudinal design.

In early-adulthood, Mareckova et al.(69) reported a quadratic association, with both higher and lower BAG associated with increased mood and anxiety symptoms. Another study reported a 0.11-year higher BAG for each unit increase of anxiety symptoms in a combined sample of

anxiety disorder, MDD, and healthy controls.(54) In middle-adulthood, three studies reported no association with estimated brain age or BAG.(40,62,70)

3.6.3 PTSD

3.6.3.1 PTSD cases

Four cross-sectional studies assessed brain age metrics in adults with PTSD. Two reported no differences in BAG or DNAm residuals. Two showed mixed findings with BAG or RNA age residuals, depending on the comparator group or brain tissue region. There were no longitudinal studies.

The one study in early-adulthood reported no difference in BAG using sMRI.(52) In middle-adulthood, three studies reported mixed results. Seeley et al.(71) compared BAG using sMRI in three groups exposed to the world trade centre bombing: individuals with PTSD, those considered highly resilient, and those with lower exposure to the event. BAG appeared decelerated (younger) in highly resilient individuals compared to those with PTSD. No difference in BAG was observed between PTSD and those with lower exposure to the event. Comparatively, no differences between a PTSD and/or MDD group and controls were reported in DNAm or RNA age residuals in the dorsolateral prefrontal cortex (dlPFC) or motor cortex; however the clinical groups had higher predicted RNA age residuals in the vmPFC.(46,47).

3.6.3.2 PTSD symptoms

One cross-sectional sMRI study in early-adulthood reported no association with BAG.(52) There were no longitudinal studies.

3.6.4 Psychological Stress

Four cross-sectional studies reported no association (*k* = 2, 50%), a positive association (*k* = 1, 25%) or mixed findings by brain age modality and metric (*k* = 1, 25%). There were no longitudinal studies.

In early-adulthood, one study used sMRI and reported no association with BAG.(72) Moon et al.(20) observed a negative relationship with BAG using sMRI and sMRI + FA but no association using FA alone. In middle-adulthood, one study reported no association with estimated brain age, while another found a positive relationship with BAG both using sMRI.(62,70)

3.6.5 Social Isolation

Cross-sectional

One study of middle-adulthood used sMRI and found a positive association with higher BAG.(39)

Longitudinal

Lay-Yee et al.(73) used sMRI and found that at 45 years old there was no difference in BAG between those socially isolated in childhood or childhood and adulthood and controls. Those isolated in only adulthood, however, had a 1.73-years higher BAG.

3.6.6 Loneliness

Cross-sectional

Three studies of early, middle or spanning early-to-middle adulthood reported no association between BAG and loneliness using sMRI and/or FA modalities.(20,39,40)

Longitudinal

A study using whole blood and an epigenetic cortical clock approach reported higher loneliness scores in middle-adulthood was associated with accelerated BAG over 11 years.(68)

3.6.7 Neuroticism

All four cross-sectional studies in early-adulthood, middle-adulthood and spanning middle-to-older adulthood reported no association with BAG or estimated brain age using sMRI and/or FA.(20,39,40,62) There were no longitudinal studies.

4. Discussion

This systematic review examined whether brain age is associated with purported psychosocial dementia risk factors, and if so, whether associations depend on risk factor, severity or life stage. From the 44 included studies, most assessed depression and none assessed

psychological trauma. A narrative synthesis was conducted, grouping studies according to risk factor and stage of adulthood.

Early Adulthood

No associations were observed between PTSD, loneliness, or neuroticism and brain age metrics in early-adulthood studies. Findings were evenly split between those reporting higher brain age in MDD and those reporting no association; associations with depressive symptoms were largely observed in studies combining MDD and healthy control participants. This pattern may suggest a threshold effect, whereby accelerated brain ageing emerges once depressive symptoms reach a clinical level. Indeed, clinical depression is more strongly associated with neuropathology and dementia risk than depressive symptoms.(74) However, longitudinal studies are needed to clarify this relationship.

Regarding anxiety, studies assessing GAD and anxiety symptoms reported positive associations with BAG; however paradoxically, anxiety symptoms and psychological stress were also associated with a lower BAG.(20,72) Mixed findings in a limited number of studies need cautious interpretation, however may suggest anxiety and psychological stress could have a neurodevelopmental impact through both delayed and accelerated brain maturation.(69) Indeed neuroimaging research has reported region-specific increased and decreased cortical thickness and volumes in young adults with anxiety.(75,76)

Middle-adulthood

No associations were observed between anxiety or neuroticism and brain age metrics in middle-adulthood; with mixed results observed with psychological stress. Two-thirds of studies reported higher brain age in MDD compared to controls, and less consistent associations were reported for depressive symptoms. One study reported an emerging association between depressive symptoms and BAG in the presence of an additional risk factor (i.e., diabetes), suggesting an additive effect of comorbidities on brain ageing,(63) and aligning with evidence that comorbid risk factors further increase dementia risk.(3) The associations observed with MDD support the Lancet Commission's report that depression in middle-age is associated with increased dementia risk.(3) However, the limited number of longitudinal studies reported mixed findings, offering little support that depression increases BAG over time.(77) The two studies (cross-sectional and longitudinal) investigating social isolation both reported accelerated brain age in middle-adulthood. Regarding loneliness, while no cross-sectional associations were observed with brain age, it was associated with greater brain age acceleration longitudinally. Both social isolation and loneliness in older-adulthood have been highlighted as risk factors for dementia, and the observation of accelerated brain ageing in middle-age may suggest that the relationship between social isolation and dementia risk may begin earlier.(78,79)

Nuanced relationships between brain age and PTSD were reported, depending on the metric and brain region studied. A higher transcriptomic brain age was observed in participants with PTSD and/or MDD in the vmPFC (but not dlPFC or motor cortex). In contrast, no association was found with epigenetic age in the same cohort and brain regions.(46) Transcriptomic ageing, which influences gene expression may be a more sensitive marker of brain ageing in PTSD as the specificity of the vmPFC aligns with a recent review implicating the ventral PFC as a neuroimaging correlate of PTSD and dementia risk.(80) As this was the only study to employ transcriptomic brain age measures, more research using this approach to examine region-specific associations with other psychosocial risks seems warranted.

Older-adulthood

Across all psychosocial risk factors, only studies examining depression were conducted with older-adults, revealing a gap in the literature, particularly regarding dementia risk. For example, no association was observed between anxiety and accelerated brain ageing in middle-adulthood however it could emerge in later life or with longitudinal follow-up. However, the small literature regarding depression does not lend strong support for that hypothesis – findings were evenly split between those reporting higher brain age in MDD and those reporting no association, and three studies spanning early-to-older adulthood found no differences. These findings could be due to a ceiling effect where age-related neurodegeneration masks the subtler effects of psychosocial stress or perhaps the biological window of influence occurs prior to older-adulthood.

General

The inconsistent findings across studies could reflect heterogeneity regarding symptom profiles, chronicity, severity and lifestyle, all of which could influence brain ageing.(41) Even different questionnaires assessing the same construct capture different symptoms. For example with depressive symptoms, Han et al.(43) reported a positive relationship with the BDI, but not with the HDRS. Indeed, many studies reported no association when using the HDRS. The BDI includes a cognitive symptom factor, while the HDRS focuses on somatic symptoms, raising the possibility that certain symptoms may differentially relate to brain ageing.(81) Repetitive negative thinking, a cognitive process characterised by difficult-to-disengage-from negative thoughts, influences the development and maintenance of depression, anxiety, neuroticism and other mental health conditions.(82) Its two core components, worry and rumination, have been associated with greater brain age.(47,62) Therefore,

general transversal psychological characteristics, potentially focused on more cognitive symptoms such as repetitive negative thinking, may be worth examining.

While this review focused primarily on psychosocial risk factors of dementia, it is also important for future research to examine the association between protective factors and brain age. In this review, Seeley et al.(71) found resilience, the ability to adapt successfully following stressful life events, was associated with a comparatively decelerated brain age in middle age.(71) This aligns with recent reviews reporting links between psychological resilience and younger brain age,(83,84) and with emerging evidence that the absence of protective psychological factors may exert greater influence on cognition and neurodegeneration than the presence of risk factors.(85)

Strengths

We employed a comprehensive systematic search strategy, including preprints and citation tracking, addressing methodological limitations of previous reviews and minimising the risk of overlooking relevant studies. We explored associations between brain age and multiple psychosocial risk factors for dementia, including cases and symptoms. Expansive inclusion of different brain age modalities allowed a comprehensive overview of divergent brain ageing processes across multiple biological levels. Adopting a life course perspective facilitated a nuanced understanding of how psychosocial risk factors relate to brain ageing, aligning with current research efforts to identify critical periods of influence.(3)

Limitations

Sparse literature focused on psychosocial factors beyond depression, older adults, or longitudinal designs, and assessment tools were heterogenous, which necessitates caution when interpreting results. Sample sizes varied, and a vote-counting approach to synthesise findings does not weight larger samples. While heterogeneity in studies precluded meta-analyses, findings from larger samples aligned with the summary of results. Demographic data were often not reported, and when they were, participants were generally middle-aged, White and from high-income countries, limiting generalisability. Future research requires more diverse populations to address the current demographic imbalance. Neuroimaging-based brain age approaches predominated, which may have contributed to variation in findings across risk factors as sMRI may capture different neurobiological processes than cellular-level changes (e.g., epigenetic ageing) that certain psychosocial factors, for example psychological stress, are hypothesised to drive.(86) Replication using approaches beyond neuroimaging are needed. Furthermore, although most studies used chronological age minus brain-predicted age, the underlying training samples, feature selection and algorithms were heterogeneous.(87) Lastly, heterogeneous biological pathways (e.g. Hypothalamic-Pituitary-Adrenal axis dysregulation, neuroinflammation, cardiovascular dysfunction) may underlie relationships between different psychosocial factors and dementia risk, and therefore impact their associations with brain age.

Conclusion

This systematic review and narrative synthesis revealed significant gaps in the literature and suggested potential patterns of associations with brain ageing across psychosocial risk factors dependent on life-stage, severity and approach. Further longitudinal research is needed to clarify the cumulative impact of these factors in older-adulthood and on dementia risk.

Declarations

Short/running title

Brain age and psychosocial risk factors for dementia

Six keywords

brain age; dementia; mental health; depression; social isolation; review

Disclosures

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Figures

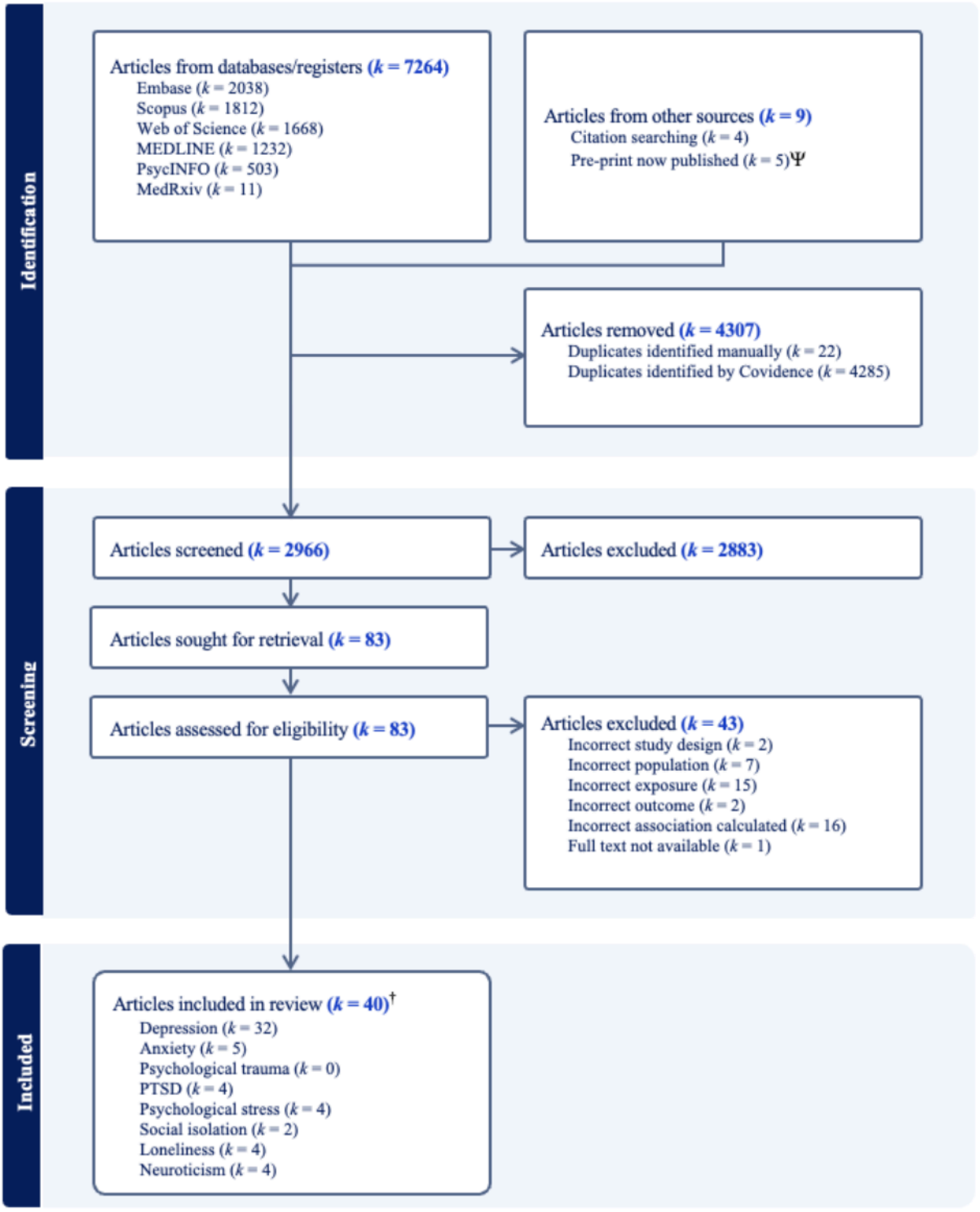


Figure 1

PRISMA flow diagram outlining the systematic review process and results of the systematic review on the association between psychosocial risk factors for dementia and brain age

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