BMJ Open

Czech Brain Aging Study (CBAS): prospective multicentre cohort study on risk and protective factors for dementia in the Czech Republic

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To cite: Sheardova K, Vyhnalek M, Nedelska Z, *et al*. Czech Brain Aging Study (CBAS): prospective multicentre cohort study on risk and protective factors for dementia in the Czech Republic. *BMJ Open* 2019;**9**:e030379. doi:10.1136/bmjopen-2019-030379

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-030379).

Received 11 March 2019
Revised 10 November 2019
Accepted 19 November 2019

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ABSTRACT

Purpose Identification of demographic, physical/physiological, lifestyle and genetic factors contributing to the onset of dementia, specifically Alzheimer disease (AD), and implementation of novel methods for early diagnosis are important to alleviate prevalence of dementia globally. The Czech Brain Aging Study (CBAS) is the first large, prospective study to address these issues in Central/Eastern Europe by enrolling non-demented adults aged 55+ years, collecting a variety of personal and biological measures and tracking cognitive function over time.

Participants The CBAS recruitment was initiated in 2011 from memory clinics at Brno and Prague University Hospitals, and by the end of 2018, the study included 1228 participants. Annual follow-ups include collection of socioeconomic, lifestyle and personal history information, neurology, neuropsychology, laboratory, vital sign and brain MRI data. In a subset, biomarker assessment (cerebrospinal fluid (CSF) and amyloid positron emission tomography) and spatial navigation were performed. Participants were 69.7±8.1 years old and had 14.6±3.3 years of education at baseline, and 59% were women. By the end of 2018, 31% finished three and more years of follow-up; 9% converted to dementia. Apolipoprotein E status is available from 95% of the participants. The biological sample bank linked to CBAS database contained CSF, serum and DNA.

Findings to date Overall, the findings, mainly from cross-sectional analyses, indicate that spatial navigation is a promising marker of early AD and that it can be distinguished from other cognitive functions. Specificity of several standard memory tests for early AD pathology was assessed with implications for clinical practice. The relationship of various lifestyle factors to cognition and brain atrophy was reported.

Future plans Recruitment is ongoing with secured funding. Longitudinal data analyses are currently being conducted. Proposals for collaboration on specific data from the database or biospecimen, as well as collaborations with similar cohort studies to increase sample size, are welcome. Study details are available online (www.cbas.cz).

Strengths and limitations of this study

- The Czech Brain Aging Study (CBAS) is a prospective longitudinal study of cognitive and brain ageing that combines prospective data on lifestyle, genetic, neuropsychological, social, physical and biological factors with neuropsychological and imaging data in the context of Alzheimer disease (AD) biomarkers.
- Although biomarkers are available for most cognitively impaired participants, only a subsample of participants with subjective memory complaints and cognitively normal controls has biomarkers available.
- Participants come from university hospital-based memory clinics from two major Czech cities—Brno and Prague—which limits generalisability, although universal healthcare coverage promotes university hospital visits by a more diverse patient population with respect to urban/rural living and socioeconomic status.
- CBAS has the potential to serve as a crucial, comprehensive source of information about markers of cognitive decline and impairment and can represent a model for studying risk/protective factors for AD in other Central and Eastern European countries.

INTRODUCTION

A gradual increase in the prevalence of dementia has been one of the trends accompanying the growth in life expectancy seen across the globe over the past few decades. Dementia affects 1% of those 60–65 years of age and about 45% of those aged 90–95 years,[1 2] although there is also evidence suggesting that the prevalence, as well as incidence of dementia, has decreased in the last decade.[3 4] This downward trend may be the result of treatment of hypertension and diabetes, as well as greater attention to lifestyle factors stemming from the increasing awareness of its impact on cognitive and overall health among the general public. Still dementia remains a major public health issue.

Currently, the course of dementia can only be modified by symptomatic therapies and no causal treatment for its most common form, Alzheimer disease (AD), or for other neurodegenerative disorders is available. A crucial step in the effective management of dementia, including AD, is to better understand the underlying neuropathological mechanisms and the differences in ethnic and lifestyle risk factors. An important effort in this context involves the identification of the extent to which demographic, physical/physiological, lifestyle and genetic factors contribute to the onset of dementia and AD specifically.

A parallel effort to searching for risk factors includes early identification of cognitive impairment. To further alleviate dementia incidence on the global level, novel diagnostic methods need to be implemented to define the risk factors for conversion from preclinical to early symptomatic (prodromal) stage and to dementia. Presumably, an early, accurate diagnosis is a crucial, yet still elusive, step in the pursuit of effective treatments for dementia.

The Czech Brain Aging Study (CBAS) is the first large, prospective study to address these issues in Eastern Europe. CBAS was designed to study potential early biomarkers and risk/protective factors of cognitive decline and dementia by enrolling a large number of older adults; collecting a variety of information about personal and family history, past and current lifestyle, genetic, physical and biological measures; and tracking cognitive function and status and brain MRI of the participants over time. The Czech Republic (CR) has approximately 150 000 patients with dementia among its roughly 10.6 million inhabitants. CR, like other Eastern European countries, is unique in a number of ways, including a relatively high prevalence of cardiovascular issues. However, since the 1980s, the frequency of common vascular risk factors is continuously decreasing, and the mortality associated with vascular risk factors in CR and neighbouring countries such as Poland has been significantly lower compared with other Eastern European countries, such as Russia. Although the cause of this remains mainly unexplained, improved prevention and education are especially suggested.[5 6]

Another unique feature of healthcare delivery in the CR is a care delivery system that favours memory clinic visits from a wide spectrum of the patient population. In turn, prodromal stages of the disease are mostly handled by neurologists, whereas postdiagnostic patients are more often seen by geriatricians and psychiatrists.[7] Neurologists generally tend to employ more sophisticated diagnostic tools for detecting early stages of cognitive deficit and assessment of its aetiology than psychiatrists/geriatricians.

Building on this model, CBAS was established using recruitment from two memory clinics at two independent neurology departments based at university hospitals in Prague and Brno, respectively. Data collection started in 2005 in Prague, and the extension to a multicenter design was possible in 2011, thanks to the European Union Regional Development Fund. The main aim of both memory clinics is to diagnose and treat neurological disorders that lead to cognitive disorders and dementia. Both centres are harmonised in terms of neuropsychological battery, multimodality MRI, positron emission tomography (PET) imaging, genetic testing, blood tests and cerebrospinal fluid (CSF) analysis, the set of questionnaires, and a participant database system.

Although CBAS lacks the advantages of a population-based study, it uses the only a currently feasible design for this type of study in the CR. In addition, it provides access to a relatively large number of clinical patients. A population-based study would need to include much larger numbers to recruit the same number of at-risk patients, which would deem the study unfeasible under the current funding mechanisms.

The overarching objectives of CBAS were to help understand lifestyle, genetic and biological factors influencing variability in the onset of cognitive impairment, including AD, and finding novel ways of early AD diagnosis. The specific aims were (1) to explore epidemiological risk factors for cognitive decline and dementia in the CR; (2) to evaluate spatial navigation and other experimental neuropsychological tests as early markers of AD pathology; (3) to define structural, metabolic and functional biomarkers of neurodegenerative diseases in older adults; and (4) to explore non-pharmacological interventions in the prevention of cognitive decline.

COHORT DESCRIPTION

Settings

CBAS is a prospective longitudinal memory clinic-based multicentre study recruiting non-demented adults 55+ years of age. Both CBAS centres work as a low-threshold facility; hence, the participants are mostly volunteers who come as a self-referral with memory complaints expressed by themselves or the family or who were referred by general practitioners, local specialists or the Czech Alzheimer Society to one of the memory clinics.

Eligibility criteria

All participants entering the two memory clinics undergo neurological examination, brain CT or MRI, and cognitive assessment, excluding subjects with dementia. All non-demented subjects aged 55+ years who are able to undergo MRI examination and are eligible (see further for exclusion criteria) are initially offered to participate in CBAS. About 95% of these subjects agreed to enter the study. The additional exclusion criteria are severe depression (participants with a recent bout of mild depression are included), a diagnosis of neurological or other psychiatric disorder, a systemic condition potentially causing cognitive impairment or a recent history of stroke. Participants referred for newly developed cognitive complaints in whom no objective cognitive deficit is found are categorised as subjective cognitive decline (SCD). Participants with objective cognitive decline are classified as mild cognitive impairment (MCI) based on

2011 National Institute on Aging and Alzheimer's Association guidelines by Albert and colleagues.[8]

Cognitively healthy controls or normal controls (NCs), defined as subjects with no significant cognitive complaints verified by memory complaints questionnaires and by a structured clinical interview and with no objective cognitive deficit, are recruited from adults taking continuing education classes under the University of the Third Age at Charles University and from relatives of employees or of study participants.

Written informed consent was obtained from each participant prior to entering the study.

Cohort characteristics

Between January 2011 and December 2018, 1228 subjects who fulfilled the CBAS criteria agreed to enter the study. Brno has contributed 496 and Prague 732 participants so far, with enrolment accelerated at both sites more recently. The basic characteristics of this cohort are presented in table 1; the frequency of vascular risk factors is in figure 1. The frequencies of these vascular risk factors in CBAS are similar to national reports and studies, almost solely conducted by cardiologists and internal medicine specialists in CR,[5] although the proportion of smokers is lower in CBAS compared with the national average reported in 2004.

Apolipoprotein E4 (apolipoprotein E (APOE) and its ε4 allele, specifically) is the strongest genetic risk factor for late-onset AD and is associated with impairments in cerebral metabolism and cerebrovascular function. About 30% of the participants carry at least one APOE ε4 allele. The dataset includes 15.2% of APOE ε4 allele heterozygotes and 5.4% homozygotes in MCI subjects, 7.2% heterozygotes and 2.1% homozygotes in SCD subjects, and only 1.2% heterozygotes in NC subjects. About 25% of the subjects are living alone, and the rest are living with a spouse, friend or a family member. All participants are community dwelling. The age of the cohort reflects the age distribution of older adults in the CR, with 12% of the subjects 80+ years of age, and 4% 85+ years of age at baseline. There are 3.3 million people aged 55+ years living in the CR, 12% of whom are 80+ years and 6% are 85+ years according to the 2018 Czech Census data. Education of our cohort is slightly higher than the average education level of 55+ population in the CR; 7.3% of the CBAS participants finished basic education (vs 26% in the CR), 68% finished secondary (high school) education (vs 62% in the CR) and 48% achieved college/university degree (vs 9% in the CR). Efforts are under way to recruit a more diverse cohort.

Aside from the CBAS cohort defined earlier, the 'CBAS Plus' database is also available, containing baseline data from 155 Brno and 283 Prague subjects who did not meet the CBAS inclusion criteria due to mild dementia of various neurodegenerative origins, depression and history of stroke and who signed informed consent. Dementia aetiology (AD dementia, frontotemporal lobar degeneration, Parkinsonian syndromes and vascular

Table 1 Basic characteristics of the Czech Brain Aging Study cohort at baseline

	Total			SCD			MCI			NC		
	Mean (SD) or ratio	Median or %	IQR	Mean (SD) or ratio	Median or %	IQR	Mean (SD) or ratio	Median or %	IQR	Mean (SD) or ratio	Median or %	IQR
Number of participants	1228			428			732			68		
Gender (M/F)	502/726	40.9% M		146/282	34.1% M		329/403	44.9% M		27/41	39.7% M	
Age (years)	69.7 (8.0)	70	64–75	67.1 (7.9)	66	61–72	71.2 (7.9)	72	66–77	68.9 (7.1)	69	64–73
Education (years)	14.6 (3.3)	14	12–17	15.2 (3.0)	15	13–18	14.3 (3.4)	13	12–17	16.1 (3.4)	16	13–17
Depression (GDS)[42]	3.86 (3.1)	3	2–5	3.9 (3.0)	3	2–5	4.0 (3.2)	3	2–6	1.6 (1.3)	1	0–1

F, female; GDS, Geriatric Depression Scale; M, male; MCI, mild cognitive impairment; NC, normal control; SCD, subjective cognitive decline.

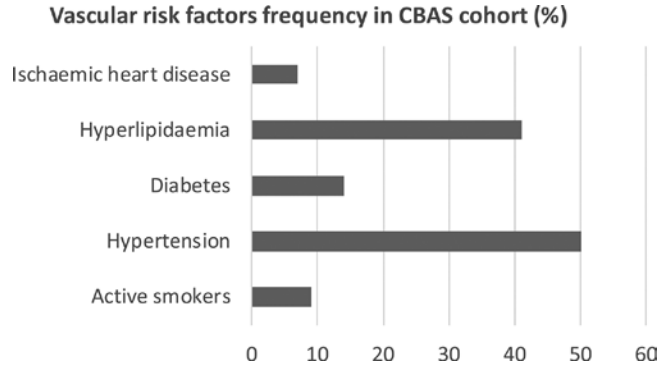

Figure 1 Frequency of vascular risk factors in the CBAS cohort. CBAS, Czech Brain Aging Study.

disorders) is diagnosed according to established guidelines.[9] The CBAS Plus cohort reflects a real memory clinic patient profile and therefore can provide clinically relevant and important data about a wide spectrum of neurological brain diseases leading to dementia and the role of vascular risk factors and psychiatric comorbidity.

Methods

At each visit, all study participants undergo a standard set of procedures. Neurological and comprehensive neuropsychology examinations, including Uniform Data Set battery, are administered[10 11]; laboratory and vital function assessments are also performed. Sociodemographic, personal, pharmacological and family history data are collected. Participants and their informants complete multiple questionnaires about cognitive complaints and lifestyle factors. MRI scans of 1.5 or 3 T are performed every 24 months or earlier when a participant converts to dementia or progresses towards cognitive impairment at an unusual rate. Volumetric MRI is analysed in all patients to obtain measures of regional cortical thickness and subcortical volumes cross-sectionally and longitudinally using Freesurfer image analysis suite V.5.3 (http://surfer.nmr.mgh.harvard.edu/). The details of Freesurfer image processing have been published elsewhere,[12–14] including previous studies by our group.[15 16] A subset of MRI volumes has been previously measured using manual tracing, and a subset of participants' MRI volumes is used to measure the atrophy of the cholinergic basal forebrain nuclei.[17] Genotyping is carried out at baseline. In a subset, CSF and/or amyloid PET is performed and additional data are collected from experimental neuropsychology, spatial navigation and personality trait assessment. The detailed procedures including their timelines are presented in table 2.

The CBAS is complemented by a biological sample bank linked to data from the CBAS and CBAS Plus cohorts. The cerebrospinal fluid (CSF) collection and storage are carried out according to the widely recognised consensus protocol for the standardisation of CSF collection and biobanking.[18] Eighteen aliquots of 0.2 mL CSF and 5–9 aliquots of serum are stored for each participant. All samples are stored at −80C. Commercial ELISA kits (Innogenetics) are used for dementia biomarker analyses (Aβ1–42, protein tau and phospho-tau), and cut-off values derived from validation study are used.[19] The characteristics of the biobank as of December 2018 are listed in table 3.

Follow-up

Participants are examined annually; they are invited for a follow-up via a letter mailed to their permanent address. Subsets of SCDs and NC who are cognitively stable for the first three visits are followed up every other year. At each follow-up visit, all participants undergo a standard set of procedures described in the Methods section; see table 2 for additional details. Standard criteria-based consensus diagnosis is performed based on each visit. MCI and dementia aetiology is based on biomarkers.[8 9]

Progression from NC/SCD to MCI or to dementia and from MCI to dementia is the main outcome, along with longitudinal quantitative measures of cognitive performance, which are used for evaluation of early markers of AD and risk factors for progression. Participants are censored when they progress to dementia as ascertained by panel consensus conference or if they can no longer undergo an MRI examination. Between entering the study and the end of 2018, 31% of the total of 1228 participants already completed at least three full yearly evaluations (baseline+2 follow-up visits) with at least two brain MRI sessions. Additionally, 9% of all participants converted to dementia at some timepoint within their follow-up and were no longer followed up, and 16% of the participants were lost to follow-up for various reasons (loss of interest, newly acquired MRI intolerance, worsening health condition and change of residence address not allowing invitation for follow-up). From all participants recruited by the end of 2018, 931 (75%) continue in the study. The recruitment is ongoing with secured funding. We have just reached a sufficient number of longitudinally followed up participants to begin with longitudinal data analyses, which will contribute significantly to the fulfilment of most of the study aims.

Patient and public involvement

Patient involvement was crucial in questionnaire implementation. Initial versions of the questionnaires were consulted with a pilot group of patients and their caregivers. Based on their feedback, we excluded McNair's questionnaire of activities of daily living. The adaptation of the Mild Behaviour Impairment Checklist was graphically reworked after being consulted, with our participants increasing the rate of successful completion considerably. In the tests developed by our team, such as the Famous Landmark Identification Test[20] or the Subjective Spatial Memory Complaints Questionnaire,[21] we consulted our participants during the entire development process, including the selection of relevant items. Some of the items were generated from qualitative research, which always preceded the development of new questionnaires. These procedures ensured high participation and validity.

Table 2 The Czech Brain Aging Study procedures

Frequency	Procedure	Specification
Annually	Clinical exam	Standard complex neurology examination
Annually	Standard neuropsychology	Uniform Data Set[10 11]: Mini-Mental State Examination, digit span forward and backward, digit symbol, Trail Making Tests A and B, animal list generation, vegetable list generation, Boston Naming Test (30 odd items), logical memory and story A Premorbid ability estimation: National Adult Reading Test[43] Memory assessment: Enhanced cued recall test,[44] Rey Auditory Verbal Learning Test,[45] Brief Visuospatial Memory Test—Revised[46] and ROCFT recall[47] Executive functions: Prague Stroop Test,[48] similarities (Wechsler Adult Intelligence Scale - Revised),[49] Controlled Oral Word Association Test,[50] Visuoconstruction: Clock Test[51] and ROCFT copy[47] Functional scales: Clinical Dementia Rating Scale[52] and Functional Assessment Questionnaire[53] Symptoms of anxiety and depression: Geriatric Depression Scale (15 items version)[42] and Beck Anxiety Inventory[54]
Annually	Laboratory	Fasting glucose, lipid profile, homocysteine, vitamin B_{12}, thyroid hormones, folic acid, renal and liver functions, C reactive protein and glycosylated haemoglobin
Annually	Vital functions	Blood pressure, pulse frequency, waist:hips ratio and Body Mass Index
Annually	Socioeconomic data	Marital status, type of living and current occupation
Annually	Questionnaires	Subjective cognitive complaints (Questionnaire de PLainte Cognitive),[55] physical/mental activity at midlife and currently, Becke's Habitual Physical Activity,[56] Epworth Sleepiness Scale[57] and Falls Self-Efficacy Scale—International[58]
Biannually	MRI	1.5T protocol: plane localiser, standard clinical T2, T1 three-dimensional isometric MPRAGE with isometric voxe, FLAIR, T2* and echoplanar imaging for diffusion tensor imaging with 32 directions 3T protocol: plane localiser; standard clinical T1 and T2; T1 three-dimensional isometric MPRAGE with isometric voxel; echoplanar imaging for diffusion tensor imaging with 64 directions; FLAIR; T2 fast spin echo; T2*; resting state functional MRI; switch to 3T MRI since 2015 in Brno, since 2019 in Prague
At baseline	Demography	Age, education, occupation and laterality
At baseline, all optional	Genotyping	Apolipoprotein E TOMM40, BDNF, CD36, BuChE, KIBRA, TREM2, PSEN 1, PSEN 2, APP, TARDBP, MAPT, GRN, C9orf72
Subset at both centres	CSF	Amyloid β-42, total, tau, p-tau, oligoclonal bands, CSF biochemistry
Subset at both centres	Amyloid PET	PET/MRI or PET/CT (visual assessment), flutemetamol, dual-phase ('perfusion') PET
Prague cohort all	Spatial navigation[22 23 27]	Hidden goal task, simple navigation task, path integration task, Y-maze assessment, intersections task, sea hero quest and spatial tasks in virtual reality/augmented virtual reality
Prague cohort optional	Experimental neuropsychology	Facial emotion recognition,[59 60] famous faces identification,[60] FNAME 12 items version,[61] Memory Binding Test[62] and spatial pattern separation task[63] In-house developed tests: Famous Landmarks Identification,[20] Episodic-like Memory Test[64] and Arena Perspective-Taking Task[65]
Brno cohort, all at baseline	Specific questionnaires	Spiritual Well-being Questionnaire,[66] OPD-2 (OPD Working Group)[67] and early life trauma assessment

CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; MPRAGE, magnetisation-prepared rapid gradient echo; OPD, Operationalized Psychodynamic Diagnostics; PET, positron emission tomography; ROCFT, Rey-Osterrieth Complex Figure Test.

Wider public engagement is ensured by public lectures regularly performed by the CBAS team members, which inform the public about the study, its goals and procedures. Partial results concerning lifestyle are discussed. The information about the study and the possibilities to join are communicated to the public via various channels, including the Concept Alzheimer Café and the CBAS webpage. We also closely cooperate with the Czech Alzheimer Association (CAA) connecting dementia specialists with patients and their caregivers. Many CAA

Table 3 Biobank characteristics

	Aliquots per patient stored at –80C	Participants (n)
Cerebrospinal fluid	18×0.2 mL	75 in Brno/350 in Prague
Serum	5–9×0.5 mL	145 in Brno/350 in Prague
DNA	Concentration>100 ng/µL	95% of all participants

members and participants of the study help disseminate information about the study, which facilitates recruitment.

FINDINGS TO DATE

Data collected from the CBAS and CBAS plus cohorts have spurred more than 60 publications so far, mainly from cross-sectional analyses, primarily in impacted neurology and neuroscience journals (the complete list is available at www.cbas.cz). We highlight the most significant ones here in the context of the aims of the study.

Early markers of AD

Spatial navigation

Spatial navigation testing is part of the baseline CBAS protocol[22 23] (for details, see table 2). Outcomes of this comprehensive examination have been compared with results of structural brain MRI and genetic and laboratory assessments. Our cross-sectional studies using clinically and biomarker-defined individuals with AD[24] have shown that spatial navigation is a distinct cognitive function and a promising cognitive marker of early stages of AD, the assessment of which may add important information to a comprehensive neuropsychological profile of individuals in the CBAS study[25 26] and may be useful for early and differential diagnosis of AD or for evaluating the effect of therapies.[27 28] This longitudinal study aimed to provide evidence for this notion. It should be noted that other copathologies may negatively impact on spatial navigation performance in individuals with AD.[29 30]

We have found that impairment of spatial navigation is associated with structural changes of the right hippocampus, entorhinal cortex, posterior parietal lobe and basal forebrain, that is, the structures that are impaired very early in AD,[15 17 25] and that it can be influenced by genetic background[31 32] and cardiovascular risk factors.[33]

Experimental neuropsychology

We have shown that our 'in-house' developed the Famous Landmarks Identification Test, created with the help from our participants, could be useful in recognising early stages of AD.[20] We have also tested the specificity of several standard memory tests for estimating hippocampal atrophy in the CBAS participants, which could have immediate implications for clinical practice.[34]

Lifestyle factors and AD

We have recently completed the first longitudinal MRI analysis from CBAS[35] showing that the level of spiritual well-being can influence the atrophy rates in regions affected by AD pathology, as well as those associated with attention and with behavioural symptoms. The manuscript is being prepared for publication. Previous studies have included examinations of cholesterol[36] and blood glucose[37] in relation to cognitive outcomes.

Non-pharmacological interventions

We have completed an intervention study with mindfulness-based stress reduction (MBSR) therapy and cognitive training in members of CBAS with MCI. We have shown that MBSR is a suitable intervention for subjects with mild cognitive decline,[38] and findings regarding its effect on cognition, immunology profile and depression suggest that MBSR could be effective in secondary prevention. The manuscript is submitted for publication.

STRENGTHS AND LIMITATIONS

CBAS represents a unique effort to study cognitive and brain ageing in Central and Eastern Europe. It is a prospective study of a relatively culturally and genetically homogenous Czech population based mainly on recruitment of volunteers who come to a memory clinic in one of the two largest cities in the country, Prague and Brno. The study includes a large biological sample bank (sera, CSF and DNA) that can enhance diagnostic accuracy and improve predictive validity of analyses with other AD risk factors, such as lifestyle factors and vascular risk factors. Despite several studies on vascular risk factors, the reasons for the high frequency of vascular problems in Eastern Europe, as well as the association between vascular factors and cognitive performance,[39] remain poorly understood. We believe that data from our study can contribute important information on this topic.

The study also has limitations. While having two sites involved in participant recruitment is an advantage, it does not create population representation. However, it is also of note that due to the nature of healthcare delivery in the CR, attendance at the two memory clinics is far from restricted to the close geographical proximity. Rather, older adults of all ages and backgrounds visit the clinics from a variety of geographical areas. This could increase the bias as usually it is the least deprived that access tertiary expertise in most healthcare settings. Therefore, coding of demographics and participant residence (urban vs rural or by region) can enrich analyses and help increase interpretability of any findings, and potentially ameliorate this limitation to at least some extent. Given the recruitment from university hospital-based clinics, one may assume that the sample could attract relatively young patients.[40] However, although the average age for patients with MCI is substantially lower than the UK-based Cognitive Function and Ageing Studies, it is roughly similar to studies from Italy, Spain

and Australia, and those studies conducted in Asia.[41] Still, results of longitudinal analyses are likely to be affected by selective attrition. Additionally, the current sample is relatively highly educated, and efforts are under way to recruit participants with more diverse educational attainment. However, there are also other advantages to basing recruitment on memory clinics, such as the access to much higher rates of at-risk patients than is typical for a population-based study, making the recruitment approach crucial in terms of study feasibility under the current CBAS funding structure.

Although brain imaging is available for most participants, biomarkers are available only for a subsample. Efforts are under way to increase biomarker data availability. Detailed information is missing on subjects lost to follow-up. Despite these limitations, to the best of our knowledge, CBAS remains the largest coordinated effort to collect longitudinal data in the context of cognitive and brain ageing in the CR and in Eastern Europe in general. CBAS is also unique in its richness of prospective data on lifestyle, genetic, neuropsychological, social, physical and biological factors as predictors of cognitive decline in the context of AD biomarkers. Until a population-based study with the same aim can be carried out within Eastern Europe, the CBAS may serve as the only source of information about a wide variety of risk factors for cognitive impairment in this geographical region.

In conclusion, CBAS has the potential to serve as a crucial, comprehensive source of information about markers of cognitive decline and impairment and can represent a model for studying risk/protective factors for AD in other Central and Eastern European countries.

Acknowledgements All of the Czech Brain Aging Study (CBAS) participants and their relatives are appreciated for their involvement in the project and their dedication. We thank the heads of neurology departments: Professor Petr Marusic from Motol University Hospital, Prague, and Professor Milan Brazdil from St. Anne's University Hospital, Brno, for their support. Big appreciation to the supporting CBAS team: neurologists and psychologists, for thorough data collection; study nurses and coordinators, for an excellent management of participants and procedures; and also external collaborators: Jitka Hanzalova Motol University Hospital, Prague, for laboratory assessment; Vaclav Matoska from Homolka Hospital, Prague; and T Freiberger from Cardiovascular and Transplant Surgery Center, Brno, for covering the DNA biobank; T Machulka and S Belaskova from ICRC, Brno, for database and statistic support. We also thank the teams from MRI and positron emission tomography facilities from university hospitals in Brno and Prague.

Contributors KS, JH, MV, JL and ZN conceived the hypothesis and the study design; KS, MV, JL, RM, JC and JH collected the data; OL, ZN and RA provided the data analyses; and RA was responsible for the statistical analyses. All authors had input on the interpretation and reporting of the study findings. KS wrote the first draft; all authors reviewed and edited the final version. All authors provided approval for the published version of the manuscript.

Funding During 2011–2015, the Czech Brain Aging Study (CBAS) was supported by the project Fakultni nemocnice u sv. Anny - International Clinical Research CentreFNUSA-ICRC (grant number CZ.1.05/1.1.00/02.0123) from the European Regional Development Fund. Between 2016 and 2020, it is supported by National Program of Sustainability II (Ministry of Education, Youth and Sports of the Czech Republic) (grant number LQ1605).The following grants contributed to specific subprojects based on CBAS: Ministry of Health Internal Grant Agency (grant number NT 11225-4/2010), Czech Health Research Council (grant numbers 16-27611A and NV18-04-00455), Motol University Hospital, Prague, Czech Republic (grant number CZ – DRO 00064203), Institutional Support of Laboratory Research (grant number 2/2012 (699002)), Institutional Support of Excellence 2nd Medical Faculty, Charles University (grant number 699012), Grant Agency of the Czech Republic (grant numbers 309/05/0693 and 309/09/1053) and Grant Agency of the Charles University (grant numbers 91007, 74308, 98509, 624012, 546113, 1108214, 135215, 654217, 308216, 546317 and 693018).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The Ethics Committee of Motol University Hospital and St. Anne's University Hospital approved the study. The cerebrospinal fluid (CSF) collection and storage are carried out after signing an informed consent in accordance with the ethical guidelines in the Czech Republic and good clinical practice.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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