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Cohort Profile: "The Czech Brain Aging Study (CBAS) – prospective multicenter cohort study on risk and protective factors for dementia in the Czech Republic"

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ABSTRACT

Purpose: To alleviate dementia prevalence globally, novel diagnostic methods need to be implemented to allow accurate early diagnosis. Another important effort is to identify demographic, physical/physiological, lifestyle, and genetic factors which contribute to the onset of dementia and Alzheimer disease specifically. The Czech Brain Aging Study (CBAS), is the first large, prospective study to address these issues in Eastern Europe by enrolling a large number of non-demented adults 55+ collecting a variety of personal and biological measures, and tracking cognitive function of the participants over time.

Participants: The recruitment is performed at Brno and Prague University Hospitals. Between January/2011-December/2018, 1228 participants entered CBAS with annual follow up. At each visit, socioeconomic data, family, personal and pharmacological history are collected. Neurology examination, neuropsychology, laboratory, vital sign assessment and MRI are performed. Multiple lifestyle and subjective cognitive complaint questionnaires are administered. In a subset, biomarker assessment (CSF, amyloid PET) and experimental psychology is performed.

Findings to date: Participants had a mean age of 69.7 ($\pm$ 8.1), mean years of education 14.6 ($\pm$ 3.3) at baseline and 59% were women. By the end of 2018, 31% of participants finished 3 and more years of follow up, 9% converted to dementia. APOE status is available from 95% of participants. Biological sample bank linked to CBAS database contains CSF, serum and DNA. Data collected so far have spurred 160 publications.

Future plans: Recruitment is on-going being co-funded by European Regional Development Fund and Ministry of Education of the Czech Republic. Longitudinal data analyses are currently being conducted. CBAS represents a unique effort to study cognitive and brain ageing in Central and Eastern Europe. Proposals for collaboration on specific data from the

database or biospecimen are welcome as well as collaborations with similar cohort studies to increase sample size. The details on CBAS are accessible on www.cbas.cz.

Key words: dementia, epidemiology, mental health

STRENGHTS AND LIMITATIONS OF THE STUDY:

- CBAS is a prospective cohort collecting longitudinal data on cognitive and brain aging combining prospective data on lifestyle, genetic, neuropsychological, social, physical and biological factors as predictors of cognitive decline in the context of AD biomarkers. All these data are connected to biobank with DNA, CSF and serum which can provide new insights into disease mechanisms and prevention
- The cohort reflects the real clinical population in a national healthcare system where everybody is insured and has an equal access to healthcare.
- 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
- Limits are provided by the specifics of Czech health care system, which is similar to Central and Eastern Europe, but different compared to US health care or UK health care. Many parallels with Western European countries.
- The weaknesses include the lack of population-based recruitment into CBAS and a current lack of biomarkers for a large proportion of participants with subjective memory complaints and for cognitively normal controls.

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 to 65 years of age and about 45% of those aged 90–95 years[1-3]. However, there is also evidence suggesting that the occurrence of dementia has slightly decreased in the last decade (data from England[4] and Stockholm[5]. These data, currently

available only from several countries, suggest a possible effect 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. Currently, the course of dementia can only be modified by symptomatic therapies and no causal treatment neither for its most common form Alzheimer disease (AD), nor for other neurodegenerative disorders, is available. A crucial step in an effective management of dementia including AD is to better understand the underlying neuropathological mechanisms, differences in ethnic and lifestyle risk factors. To alleviate dementia prevalence on the global level substantially, beyond the modest improvements seen recently, novel diagnostic methods need to be implemented to define the risk factors for conversion from preclinical to early symptomatic (prodromal) stage and further to dementia. Presumably, an early, accurate diagnosis is a crucial, yet still elusive, step in the pursuit of effective treatments for dementia. Another 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.

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. Czech Republic (CR) has approximately 150 000 people with dementia per 10.6 million inhabitants. In CR, prodromal stages of the disease are mostly handled by neurologists, who tend to employ more sophisticated diagnostic tools in differential diagnosis of dementia. Geriatricians and psychiatrists usually diagnose and treat patients at the stage of full-blown dementia[6]. Building on this clinical model, CBAS

incorporates two independent clinical sites: Memory clinics based at university hospitals in Prague and Brno. Data collection started 2005 in Prague and the extension to a multicentric 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 centers are harmonized in terms of the neuropsychological battery, multimodality magnetic resonance imaging (MRI), PET imaging, genetic testing, blood tests and cerebrospinal fluid (CSF) analysis and they use the same questionnaires and participant database system.

The primary objectives of CBAS are: 1. Exploring epidemiological risk factors for cognitive decline and dementia in the Czech population; 2. Evaluation of spatial navigation and other experimental neuropsychological tests as early markers of AD pathology; 3. Defining structural, metabolic and functional biomarkers of neurodegenerative diseases in older adults; and 4. Utilizing non-pharmacological interventions in prevention of cognitive decline.

COHORT DESCRIPTION

Settings

CBAS is a prospective longitudinal memory clinic based multi-center study recruiting non-demented adults 55+ years of age. Both CBAS centers 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 were referred by general practitioners, local specialists or Czech Alzheimer Society to one of the memory clinics. Cognitively healthy controls are recruited by advertising among healthy geriatric population.

Eligibility Criteria

All subjects undergo standardized 1.5T or 3T MRI, neuropsychological protocol including Uniform Data Set (UDS)[7,8] battery and neurological examination. Standard criteria-based consensual diagnosis classifies subjects as cognitively normal controls (NC), subjective

cognitive decline (SCD), mild cognitive impairment (MCI) or dementia. NC are defined as subjects with no objective cognitive deficit and no significant subjective cognitive complaints verified by memory complaints questionnaires and structured clinical interview. Subjects referred for newly developed cognitive complaints in which no objective cognitive deficit is found are categorized as SCD. Patients with MCI are diagnosed and classified based on Albert's NIA-AA guidelines 2011[9]. Classification of MCI etiology is based on biomarkers. All non-demented subjects aged 55 and older who are classified as NC, SCD or MCI are initially offered to participate in the CBAS. About 95% of these subjects agreed to enter the study. Control participants with no cognitive complaints are recruited from adults taking continuing education classes under the University of the Third Age at Charles University, 2nd Medical Faculty, and from relatives of employees or of the study participants. Written informed consent was obtained from each participant prior entering the database. The Ethics Committee of Motol University Hospital and St. Anne´s University Hospital approved the research study.

The additional exclusion criteria are severe depression (a recent bout of mild depression is not an exclusion criterion) or other neurological or psychiatric disorder or systemic condition potentially causing cognitive impairment. Subjects with a history of stroke are excluded. Aside from the CBAS cohort defined as above, baseline data are available from 155 Brno/ 283 Prague subjects who did not meet the CBAS inclusion criteria labelled as cohort "CBAS Plus"- i.e. patients with mild dementia of various neurodegenerative origin, depression, history of stroke etc. Dementia etiology (AD dementia, frontotemporal lobar degeneration, Parkinsonian syndromes, vascular disorders etc.) is diagnosed according to appropriate guidelines[10,11]. CBAS Plus cohort reflects real memory clinic patient profile and therefore can provide clinically relevant and important research data about wide spectrum of

neurological brain diseases leading to dementia and the role of vascular risk factors and psychiatric co-morbidity.

Cohort Characteristics

Between January 2011- December 2018, 1228 subjects who fulfilled the CBAS criteria agreed to enter the study with the contribution of 496 from Brno and 732 from Prague. The basic characteristics of this cohort are presented in table 1, the frequency of vascular risk factors in figure 1. Apolipoprotein E4 (APOE 4) 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 4 allele, the frequency of APOE 4 according to baseline diagnosis is presented in figure 2. About 25% of the subjects are living alone and the rest are living with spouse friend, or a family member. Marital status distribution among the participants see in figure 3.

Table 1. The basic characteristics of the CBAS cohort at baseline

	Total	SCD	MCI	NC
No. of participants	1228	428	732	68
Gender (M/F)	502/726	146/282	329/403	27/41
Age/years	69.7 (8.1)	67.1 (7.9)	71.2 (7.9)	68.9 (7.1)
Education/years	14.6 (3.3)	15.2 (3.0)	14.2 (3.4)	15.9 (3.2)
Depression (GDS score)	3.1 (3.1)	2.9 (3.0)	3.3 (3.2)	1.6 (2.1)

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 3 visits are followed up biannually. At the baseline as well as at each follow-up visit, all participants undergo a comprehensive multidisciplinary examination. Consensual diagnosis is performed based on each visit. 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. Between entering the study and the end of 2018, 31% of the participants completed at least 3 assessments (baseline + 2 follow up visits), 9% converted to dementia and 16% were lost to follow up. The recruitment is still on going.

Methods

At each visit, all study participants undergo a standard set of procedures. Neurological and comprehensive neuropsychology examination, laboratory and vital functions assessments are performed. Socio-demographic data, personal, pharmacological and family history is obtained. Participants and their informers complete multiple questionnaires about cognitive complaints and lifestyle factors. 1.5T or 3T MRI scans are performed every 24 months and when a participant converts to dementia or progresses towards cognitive impairment at an unusual rate. Volumetric MRI is analyzed in all patients to obtain measures of regional cortical thickness and subcortical volumes cross-sectionally and longitudinally using Freesurfer image analysis suite (v5.3; http://surfer.nmr.mgh.harvard.edu/). The details of Freesurfer image processing have been published elsewhere[12-17], including previous studies by our group[18,19]. 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 cholinergic basal forebrain nuclei[20,21]. 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 are presented in Supplementary table S1.

The CBAS is complemented by a biological sample bank linked to the data from the CBAS and "CBAS Plus" cohorts. The CSF collection and storage are carried out after signing an informed consent in accordance with the ethical guidelines in the CR and good clinical practice, and according to the widely recognized consensus protocol for the standardization of

cerebrospinal fluid collection and biobanking [22]. 18 aliquots of 0.2ml 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[23]. The characteristics of the biobank as of December 2018 are listed in table 2.

Table 2. Biobank characteristics

	Aliquots stored at -80C	No. of participants
CSF	18x0.2ml	75 Brno/350 Prague
Serum	5-9x0.5ml	145 Brno/350 Prague
DNA	concentration >100 ng/µl	95% of all participants

Patient and public involvement

Patient involvement was crucial in questionnaire implementation. Initial versions of questionnaires were largely consulted with a pilot group of patients. Their caregivers and their remarks and feedback were considered when making the final version to ensure better understanding and participation. Wider public engagement is ensured by public lectures regularly performed by the CBAS team members, informing about the study, its meaning and procedures; partial results concerning lifestyle are discussed. The information about the study and possibility to join is communicated to public via various channels: Concept Alzheimer Café, CBAS webpage, we also closely cooperate with Czech Alzheimer Association (CAA) connecting dementia specialists with patients and their caregivers. Many CAA layperson members and participants of the study helped to disseminate the baseline information which helped to strengthen the recruitment.

FINDINGS TO DATE

The CBAS medical and non-medical personnel participate in academic and research activities. Data collected so far have spurred more than 160 publications, primarily in impacted neurology and neuroscience journals. We highlight the most significant ones here.

Spatial navigation as an early marker of AD

Our unique assessment instrument, the real-space human analogue of the Morris water maze called the Blue velvet arena, plus its computerized equivalent, test separately the hippocampal-dependent allocentric and the parietal lobe-dependent egocentric types of navigation[24]. Results so far have demonstrated that the tool, especially its component testing allocentric navigation, may serve as an important early marker of cognitive impairment and AD[25]. In the scope of CBAS we have demonstrated a strong association between real-space and computer-based versions of this test, which further shifts the importance of our research towards the routine clinical use[26]. The relationship between spatial navigation and brain structures in patients with mild AD dementia and amnestic MCI (aMCI) was investigated in our other studies. In the first study, we demonstrated a direct relation between right hippocampal volume and allocentric navigation above and beyond total brain and left hippocampal volumes in real-space and computer-based versions of the test[18]. In another study, we demonstrated a direct relationship between basal forebrain volume and allocentric navigation above and beyond hippocampal volume, again in both versions of the test[20]. Together, these findings provide physiological evidence for the internal validity of the spatial navigation test.

We have also demonstrated that spatial navigation performance in aMCI patients is influenced by their genetic background. We showed that spatial navigation deteriorates in a dose-dependent manner as a function of APOE ε4 status[27] and that especially allocentric navigation is impaired in individuals with APOE ε3/ε3 (AD risk neutral) genotype, who carry TOMM40 "523" VL variants[28]. Our findings thus indicate that spatial navigation performance can identify aMCI patients at an increased genetic risk for AD. Spatial navigation has potential not only in early and differential diagnostics, but also as an outcome measure to evaluate treatment effect[29]. In addition, we have linked cardiovascular biomarkers, namely

elevated homocysteine and total cholesterol levels to spatial navigation deficits in our recent study[30].

Our other studies have found that, besides the egocentric and allocentric types of navigation, navigation without vision (path integration) and perspective taking also identify patients with mild AD dementia and aMCI among a general sample[31,32]. In sum, spatial navigation is a promising psychological marker of early AD, which may be distinguished from other cognitive functions, and thus its assessment is likely to contribute important information to a comprehensive neuropsychological profile[33].

Experimental neuropsychology helping to find patients at early stage of AD

In the scope of examination of the affected medial temporal structures we have used "in-house" developed Familiar Landmarks identification test together with the validated Facial Emotion Recognition and Identification of Familiar Faces tests[34,35]. We suggested that recognition of different categories of objects might reflect different stages of AD pathology from transentorhinal cortex through amygdala to fusiform gyrus as it is described in neuropathological studies[36,37].

We have also tested the specificity of several standard memory tests for reflecting hippocampal atrophy in non-demented geriatric population. The Enhanced Cued Recall test with controlled encoding and cued recall, designed to detect hippocampal dysfunction, did not exceed the standard memory tests. In the non-demented population we therefore did not confirm the hypothesis of greater selectivity of the tests with controlled encoding and cued recall paradigm to detect the damage of hippocampus. The result has immediate implications for clinical practice [38]. Initial longitudinal data analyses are currently being conducted.

STRENGHTS AND LIMITATIONS

CBAS represents a unique effort to study cognitive and brain ageing in Central and Eastern Europe. It is a prospective cohort, based in a relatively culturally and genetically homogenous Czech population. The location of the two CBAS centers in the two main regions of the CR (Bohemia and Moravia) allows to cover practically the whole country. To our best knowledge it is the first and only coordinated clinically based study collecting longitudinal data on cognitive and brain aging combining prospective data on lifestyle, genetic, neuropsychological, social, physical and biological factors as predictors of cognitive decline in the context of AD biomarkers in CR and Eastern Europe and among a few studies globally. The weaknesses include the lack of population-based recruitment into CBAS; the current lack of biomarkers for a large proportion of participants with subjective memory complaints and for cognitively normal controls; and the lack of information regarding those who refused to participate. However, the cohort reflects the real clinical population in a national healthcare system where everybody is insured and has an equal access to healthcare.

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.

COLLABORATION

We have established a cohort which allows for integration of multiple clinical data with biomarkers and lifestyle factors. All these data are connected to biobank with DNA, CSF and serum which can provide new insights into disease mechanisms and prevention. The details about the study are accessible on www.cbas.cz. We encourage collaborations with researchers from other cohort studies with similar aspects to increase sample size.

Proposals for collaboration on specific data from the database or biospecimen (DNA, CSF, serum) are welcome. All proposals for specific analyses are reviewed by a scientific

committee. For more information, please contact the corresponding author and/or the Principal Investigator through email: sheardova@fnusa.cz, jakub.hort@fnmotol.cz

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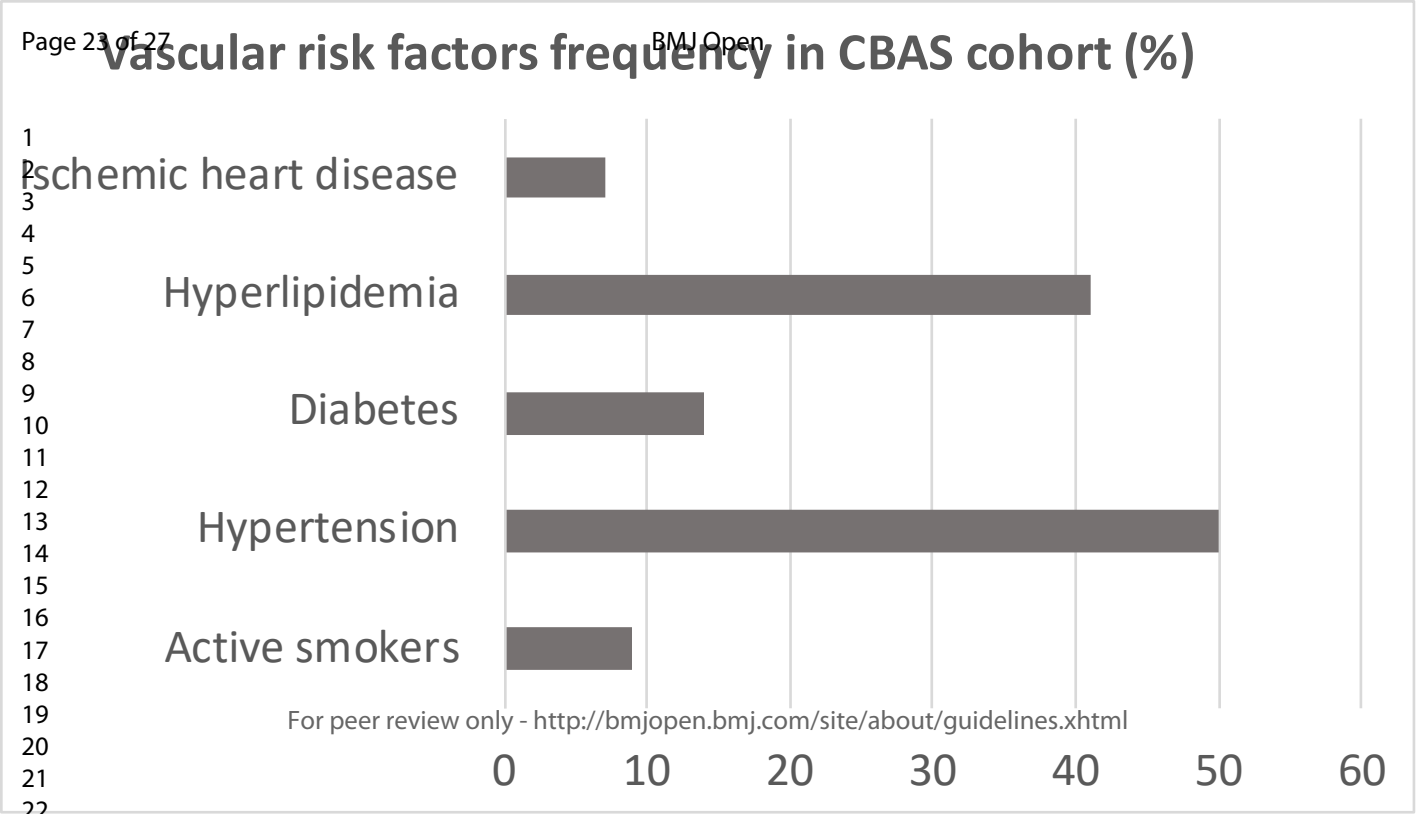
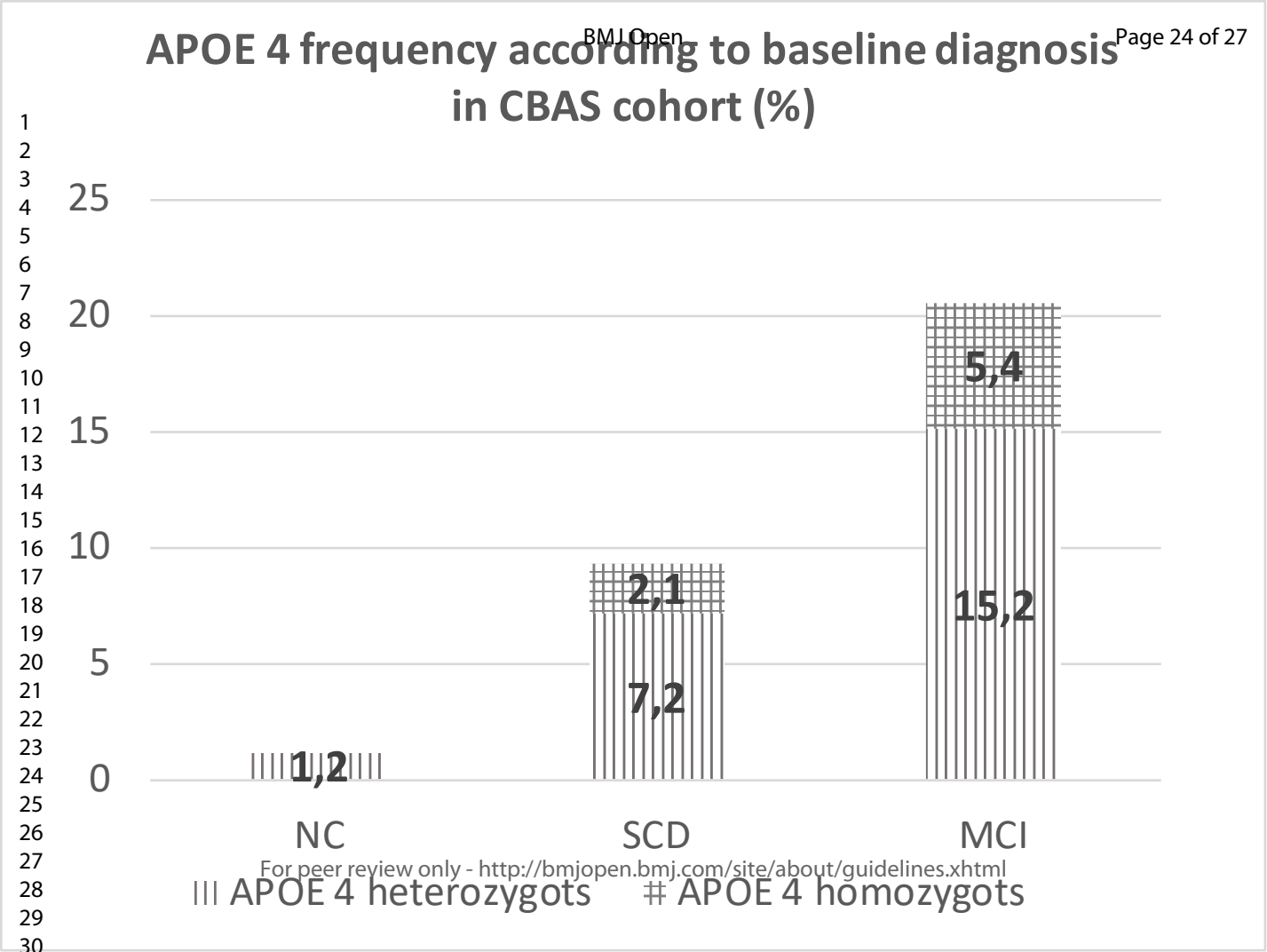
Figure legends:

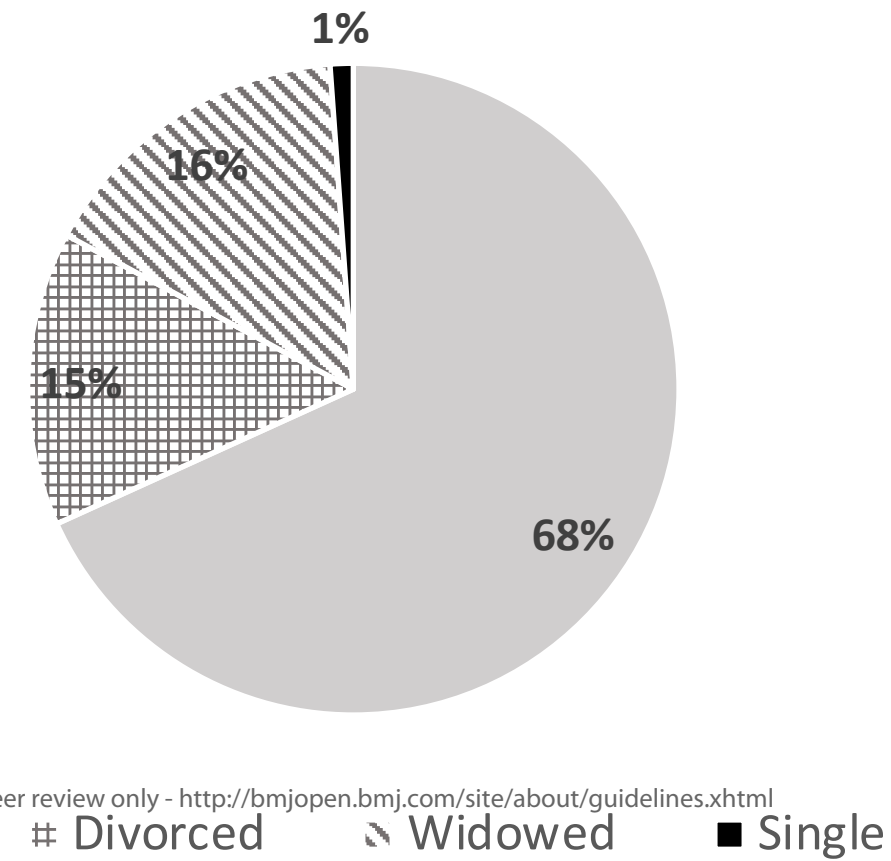
Figure 1 The frequency of vascular risk factors in CBAS cohort

Figure 2 APOE 4 status according to baseline diagnosis in the CBAS cohort

Figure 3 Marital status of the CBAS participants







Supplementary table S1. Procedures performed within the study (frequency is specified)

Frequency	Procedure	Specification
Annually	Clinical exam	Standard complex neurology examination
Annually	Standard neuropsychology	**Uniform Data Set**[7,8]: MMSE, Digit Span Forward and Backward (WMS-R), Digit Symbol (WAIS-R), Trail Making Test A and B, Animal list generation, Vegetable list generation, Boston Naming Test (30 odd items), Logical Memory, Story A (WMS-R) **Premorbid ability estimation**: National Adult Reading Test[39] **Memory assesment:** Enhanced cued recall test[40], Rey Auditory Verbal Learning test[41], Brief Visuospatial Memory Test–Revised[42], Rey-Osterrieth Complex Figure Test – (ROCFT) recall[43] **Executive functions**: Prague Stroop test[44], Similarities (WAIS-R)[45], Controlled Oral Word Association Test[46] **Visuoconstruction**: Clock Test[47], ROCFT copy[43] **Functional scales**: Clinical dementia rating scale[48], Functional assessment questionnaire[49] **Symptoms of anxiety and depression**: Geriatric depression scale (15 items version)[50], Beck anxiety inventory[51]
Annually	Laboratory	Fasting glucose, lipids, homocysteine, B12, thyroid hormones, folic acid, renal and liver function, CRP, glycosylated haemoglobin
Annually	Vital functions	BMI, blood pressure, pulse, waist/hipps ratio
Annually	Socio- economic data	Marital status, Type of living, Current occupation
Annually	Questionnaires	Subjective cognitive complaints (QPC)[52], physical/mental activity at midlife and now, Becke's Habitual Physical Activity[53], Epworth Sleepiness Scale[54], Falls Self-Efficacy Scale – International[55]
Biannually	MRI	1.5T protocol: plane localizer; standard clinical T2; T1 3-dimensional isometric magnetization-prepared rapid gradient echo(MPRAGE) with isometric voxel;fluid-attenuated inversion recovery(FLAIR); T2*; echoplanar imagingfor diffusion tensor imaging with 32directions.3T protocol: plane localizer; standardclinical T1 and T2; T1

		3-dimensional isometric magnetization-prepared rapid gradient echo (MPRAGE) with isometric voxel; echoplanar imaging for diffusion tensor imaging with 64 directions; fluid-attenuated inversion recovery (FLAIR); T2 fast spin echo;T2*; resting state functional MRimaging. 3T MRI switch since 2013 in Brno, since 2019 in Prague
At baseline	Demography	Age, education, occupation, laterality
At baseline all Optional	Genotyping	APOE TOMM40, BDNF, CD36, BuChE, KIBRA, TREM2, PSEN 1, PSEN 2, APP, TARDBP, MAPT, GRN, C9orf72
Subset at both centres	CSF	Amyloid, tau, ptau, 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[24-26]	hidden goal task, simple navigation task, path integration task, Y-maze assessment, intersections task, sea hero quest, spatial tasks in virtual reality/augmented virtual reality
Prague cohort optional	Experimental neuropsychology	Facial emotion recognition[35], Famous faces identification[34], FNAME 12 items version[56], Memory binding test[57], spatial pattern separation task[58] In house invented - Famous landmarks identification[36], episodic-like memory test[59], Arena Perspective Taking Task[60]
Brno cohort All at baseline	Specific questionnaires	Spiritual well-being questionnaire (SHALOM)[61], Operationalized Psychodynamic Diagnostics OPD-2 (OPD working group)[62], early life trauma assessment

MMSE – Minimental state examination, WMS-R -Wechsler Memory Scale Revised[63], WAIS-R - Wechsler Adult Intelligence Scale-Revised[45]

BMJ Open

Cohort Profile: "The Czech Brain Aging Study (CBAS) – prospective multicenter cohort study on risk and protective factors for dementia in the Czech Republic"

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Cohort Profile: "The Czech Brain Aging Study (CBAS) – prospective multicenter cohort study on risk and protective factors for dementia in the Czech Republic"

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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+, collecting a variety of personal and biological measures, and tracking their cognitive function over time.

Participants: The CBAS recruitment was initiated in 2011 from memory clinics at Brno and Prague University Hospitals, and by end of 2018, the study included 1228 participants. Annual follow-ups include collection of socioeconomic and personal history, neurology, neuropsychology, laboratory, vital sign assessment and brain MRI. Multiple lifestyle questionnaires are administered. In a subset, biomarker assessment (CSF, amyloid PET) and spatial navigation are performed. Participants are of average age of 69.7±8.1 years and 14.6±3.3 years of education at baseline, and 59% are women. By the end of 2018, 31% finished 3 and more years of follow up, 9% converted to dementia. APOE status is available from 95% of participants. Biological sample bank linked to CBAS database contains 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 which may 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 life-style factors to cognition and brain atrophy was reported.

Future plans: Recruitment is on-going with secured funding. Longitudinal data analyses are currently being conducted. Proposals for collaboration on specific data from the database or

biospecimen are welcome as well as collaborations with similar cohort studies to increase sample size. The details are accessible on www.cbas.cz.

Key words: dementia, epidemiology, mental health

STRENGHTS AND LIMITATIONS OF THE STUDY:

- CBAS is a prospective longitudinal study of cognitive and brain aging that combines prospective data on lifestyle, genetic, neuropsychological, social, physical and biological factors with neuropsychological and imaging data in the context of AD biomarkers.
- Although biomarkers are available for most cognitively impaired participants, only a subsample of participants with subjective memory complaints and of cognitively normal controls has biomarkers available.
- Participants come from university hospital-based memory clinics from two major Czech cities—Brno and Prague—which limits generalizability, although universal health care coverage promotes university hospital visits by a more diverse patient population.
- 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 to 65 years of age and about 45% of those aged 90–95 years.[1, 2] However, there is also evidence suggesting that the prevalence as well as incidence of dementia has significantly decreased in the last decade - data from England[3] and Stockholm.[4] These data, currently available only from several countries, suggest a possible effect 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. 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 an 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 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. 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 eighties of the 20th century, the frequency of common vascular risk factors is continuously decreasing in CR, and the mortality associated with vascular risk factors in CR and neighboring countries such as Poland has been significantly

lower compared to other Eastern European countries, such as Russia. Although the cause of this remains mainly unexplained improved prevention and education are especially suggested.[5, 6] Also a system of health care delivery that favors memory clinic visits from a wide variety of patient population is rather specific. In CR, prodromal stages of the disease are mostly handled by neurologists, whereas post-diagnostic patients are more often seen by geriatricians and psychiatrists.[7] In general, neurologists tend to employ more sophisticated diagnostic tools for detecting early stages of cognitive deficit and assessment of its etiology 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 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 centers are harmonized in terms of the neuropsychological battery, multimodality magnetic resonance imaging (MRI), PET imaging, genetic testing, blood tests and cerebrospinal fluid (CSF) analysis, the use of questionnaires, and a participant database system.

Although CBAS lacks the advantages of a population-based study, it uses the only 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 not feasible under the current funding mechanisms.

The overarching objectives of CBAS are 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 are: 1. Exploring epidemiological risk

factors for cognitive decline and dementia in the Czech Republic; 2. Evaluation of spatial navigation and other experimental neuropsychological tests as early markers of AD pathology; 3. Defining structural, metabolic and functional biomarkers of neurodegenerative diseases in older adults; and 4. Exploring non-pharmacological interventions in prevention of cognitive decline.

COHORT DESCRIPTION

Settings

CBAS is a prospective longitudinal memory clinic based multi-center study recruiting non-demented adults 55+ years of age. Both CBAS centers 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 Czech Alzheimer Society to one of the memory clinics. Cognitively healthy controls are recruited by advertising among general older population and including those with no cognitive complaints, including participants recruited from adults taking continuing education classes under the University of the Third Age at Charles University, 2nd Medical Faculty, and from relatives of employees or study participants.

Eligibility Criteria

All participants entering the memory clinics undergo neurological examination, brain CT or MRI, and cognitive assessment, excluding subjects with dementia. All non-demented subjects aged 55 and older who are able to undergo MRI examination and do not fulfill exclusion criteria (see below) are initially offered to participate in the 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.

Written informed consent was obtained from each participant prior entering the database. The Ethics Committee of Motol University Hospital and St. Anne´s University Hospital approved the study.

Cohort Characteristics

Between January 2011and December 2018, 1228 subjects who fulfilled the CBAS criteria agreed to enter the study with the contribution of 496 from Brno and 732 from Prague, with enrollment accelerated 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 to national average reported in 2004.

Table 1. Basic characteristics of the CBAS cohort at baseline

	Total			SCD			MCI			NC		
	mean (SD) or ratio	median or %	Inter quartile range	mean (SD) or ratio	median or %	Inter quartile range	mean (SD) or ratio	median or %	Inter quartile range	mean (SD) or ratio	median or %	Inter quartile range
No. 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)	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

Notes: SCD = subjective cognitive decline; MCI = mild cognitive impairment; SD = standard deviation; GDS = Geriatric Depression Scale[8]

Apolipoprotein E4 (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 frequency of APOE ε4 allele assessed at baseline was – 15.2% 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. 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+ living in the CR, 12% of whom are 80+ and 6% are 85+ according to 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 CR), 68% finished secondary (high school) education (vs. 62% in CR) and 48% achieved college/university degree (vs. 9% in CR). Efforts are under way to recruit a more diverse cohort.

Aside from the CBAS cohort defined above, baseline data are available from 155 Brno/ 283 Prague subjects who did not meet the CBAS inclusion criteria under the name "CBAS Plus"- i.e. patients with mild dementia of various neurodegenerative origin, depression, history of stroke etc. Dementia etiology (AD dementia, frontotemporal lobar degeneration, Parkinsonian syndromes, vascular disorders etc.) is diagnosed according to appropriate guidelines.[9] CBAS Plus cohort reflects a real memory clinic patient profile and therefore can provide clinically relevant and important research data about a wide spectrum of neurological brain diseases leading to dementia and the role of vascular risk factors and psychiatric co-morbidity.

Methods

At each visit, all study participants undergo a standard set of procedures. Neurological and comprehensive neuropsychology examination including Uniform Data Set (UDS) battery,[10, 11] laboratory and vital functions assessments are also performed. Socio-demographic, personal, pharmacological and family history data are obtained. Participants and their informants complete multiple questionnaires about cognitive complaints and lifestyle factors. 1.5T or 3T MRI scans 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 analyzed in all patients to obtain measures of regional cortical thickness and subcortical

volumes cross-sectionally and longitudinally using Freesurfer image analysis suite (v5.3; 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 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.

Table 2. The CBAS 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 Test A and B, Animal list generation, Vegetable list generation, Boston Naming Test (30 odd items), Logical Memory, Story A **Premorbid ability estimation**: National Adult Reading Test[18] **Memory assessment:** Enhanced cued recall test,[19] Rey Auditory Verbal Learning Test,[20] Brief Visuospatial Memory Test–Revised,[21] Rey-Osterrieth Complex Figure Test – (ROCFT) recall[22] **Executive functions**: Prague Stroop test,[23] Similarities (WAIS-R)[24], Controlled Oral Word Association Test[25] **Visuoconstruction**: Clock Test,[26] ROCFT copy[22] **Functional scales**: Clinical Dementia Rating scale,[27] Functional assessment questionnaire[28] **Symptoms of anxiety and depression**: Geriatric Depression Scale (15 items version),[8] Beck Anxiety Inventory[29]
Annually	Laboratory	Fasting glucose, lipid profile, homocysteine, vitamin B12, thyroid hormones, folic acid, renal and liver function, C-reactive protein, glycosylated hemoglobin
Annually	Vital functions	blood pressure, pulse frequency, waist/hips ratio, BMI
Annually	Socio- economic data	Marital status, Type of living, Current occupation
Annually	Questionnaires	Subjective cognitive complaints (QPC),[30] physical/mental activity at midlife and currently, Becke's Habitual Physical

		Activity[31], Epworth Sleepiness Scale,[32] Falls Self-Efficacy Scale – International[33]
Biannually	MRI	1.5T protocol: plane localizer; standard clinical T2; T1 3-dimensional isometric magnetization-prepared rapid gradient echo(MPRAGE) with isometric voxel; fluid-attenuated inversion recovery(FLAIR); T2*; echoplanar imaging for diffusion tensor imaging with 32directions.3T protocol: plane localizer; standard clinical T1 and T2; T1 3-dimensional isometric magnetization-prepared rapid gradient echo (MPRAGE) with isometric voxel; echoplanar imaging for diffusion tensor imaging with 64 directions; fluid-attenuated inversion recovery (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, laterality
At baseline all Optional	Genotyping	APOE 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[34, 35, 36]	hidden goal task, simple navigation task, path integration task, Y-maze assessment, intersections task, sea hero quest, spatial tasks in virtual reality/augmented virtual reality
Prague cohort optional	Experimental neuropsychology	Facial emotion recognition,[37, 38] Famous faces identification,[38] FNAME 12 items version,[39] Memory binding test,[40] spatial pattern separation task[41] In house developed tests: Famous landmarks identification,[42] episodic-like memory test,[43] Arena Perspective Taking Task[44]
Brno cohort All at baseline	Specific questionnaires	Spiritual well-being questionnaire (SHALOM),[45] Operationalized Psychodynamic Diagnostics OPD-2 (OPD working group),[46] early life trauma assessment

Standard criteria-based consensus diagnosis classifies subjects as cognitively normal controls (NC), subjective cognitive decline (SCD) or mild cognitive impairment (MCI). NC are defined as subjects with no objective cognitive deficit and no significant subjective cognitive complaints verified by memory complaints questionnaires and a structured clinical interview. Subjects referred for newly developed cognitive complaints in which no objective cognitive

deficit is found are categorized as SCD. Patients with MCI are diagnosed and classified based on 2011 NIA-AA guidelines by Albert and colleagues.[47] Classification of MCI etiology is based on biomarkers.

The CBAS is complemented by a biological sample bank linked to data from the CBAS and "CBAS Plus" cohorts. The CSF collection and storage are carried out after signing an informed consent in accordance with the ethical guidelines in the CR and good clinical practice, and according to the widely recognized consensus protocol for the standardization of cerebrospinal fluid collection and biobanking.[48] Eighteen aliquots of 0.2ml 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.[49] The characteristics of the biobank as of December 2018 are listed in table 3.

Table 3. Biobank characteristics

	Aliquots per patient stored at -80C	No. of participants
CSF	18x0.2ml	75 in Brno/350 in Prague
Serum	5-9x0.5ml	145 in Brno/350 in Prague
DNA	concentration >100 ng/µl	95% of all participants

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 3 visits are followed 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. Consensus diagnosis is performed based on each visit. 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 no longer can undergo an MRI examination. Between entering the study and the end of 2018, 31% of the total of 1228 participants already completed at least 3 full yearly evaluations (baseline + 2 follow up visits) with at least 2 brain MRI sessions. 9% from all the participants converted to dementia at some timepoint within their follow-up and were no longer followed, and 16% of the participants were lost to follow-up for various reasons (loss of interest, newly acquired MRI intolerance, worsening health condition, change of residence address not allowing invitation for follow up. From all participants recruited by the end of 2018, 931 (75%) continue in the follow-up. The recruitment is still ongoing.

Patient and public involvement

Patient involvement was crucial in questionnaire implementation. Initial versions of 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 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[42] or the Subjective Spatial Memory Complaints Questionnaire,[50] 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.

Wider public engagement is ensured by public lectures regularly performed by the CBAS team members, informing about the study, its meaning and procedures; partial results concerning lifestyle are discussed. The information about the study and possibility to join is communicated to public via various channels: Concept Alzheimer Café, CBAS webpage, we also closely cooperate with Czech Alzheimer Association (CAA) connecting dementia

specialists with patients and their caregivers. Many CAA layperson members and participants of the study help disseminate information about the study which facilitates recruitment.

FINDINGS TO DATE

Data collected so far have spurred more than 160 publications 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 baseline CBAS protocol[34, 35] (details see in table 2). Outcomes of this comprehensive examination have been compared with results of structural brain MRI and genetic and laboratory assessment. Our cross-sectional studies have shown that spatial navigation is a distinct cognitive function and a promising cognitive marker of early AD, the assessment of which may add important information to a comprehensive neuropsychological profile of individuals in the CBAS study[51, 52] and may be useful for early and differential diagnosis of AD, or for evaluating the effect of therapies.[36, 53]

We have demonstrated that impairment of spatial navigation is associated with structural changes of the right hippocampus, entorhinal cortex, posterior parietal lobe and basal forebrain, i.e. the structures that are impaired very early in AD[15, 17, 51] and that it can be influenced by genetic background[54, 55] and cardiovascular risk factors.[56]

Experimental neuropsychology

We have introduced our “in-house” developed Famous Landmarks Identification Test which was created with the help of our participants and we have shown that it could be useful for recognizing early stages of AD.[42] We have also tested the specificity of several standard

memory tests for reflecting hippocampal atrophy in the CBAS participants which could have immediate implications for clinical practice.[57]

Lifestyle factors and AD

We have recently completed the first longitudinal MRI analysis from CBAS[58] showing that the level of spiritual well-being can influence the atrophy rates in regions affected by AD pathology, associated with attention and with behavioral symptoms. The manuscript is being prepared for publication. Previous studies have included examinations of cholesterol[59] and blood glucose[60] in relation to cognitive outcomes.

The recruitment is ongoing with secured funding. We have just reached a sufficient number of longitudinally followed participants to begin with longitudinal data analyses which will contribute significantly to the fulfillment of most of the aims of the study.

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[61] 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.

STRENGHTS 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 two largest cities in the country-Prague and Brno. The study includes a large biological sample bank (sera, CSF, 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 of several studies on vascular risk factors, it has not been satisfactorily

explained yet why is their frequency so high in Eastern Europe and to which extend are they associated with cognitive performance.[62] We believe that data from our study can also contribute to the information about this subject.

The study also has limitations. While having two sites involved in participant recruitment is an advantage, it cannot compete with a population-based recruitment. Although it is also of note that due to the nature of health care delivery in the CR, attendance of the two memory clinics is far from restricted to the close geographical proximity. Rather, older adults of all ages visit the clinics from a variety of geographical areas. Therefore, coding of 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.[63] However, although the average age for patients with MCI is substantially lower than the UK-based Cognitive Function & Ageing Studies, it is roughly similar to studies from Italy, Spain, Australia, and studies conducted in Asia.[64] Additionally, the current sample is relatively highly educated and efforts are under way to recruit participants with more diverse educational attainment. There are also advantages to basing recruitment on memory clinics. Specifically, this approach allows access to at-risk patients at a much higher rate than a population-based study, making the approach more feasible 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 aging in the Czech Republic 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.

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FOOTNOTES:

Patient consent for publication: Not required

Contributors: KS, JH, MV, JL and ZN conceived the hypothesis and study design, KS, MV, JL, RM, JC, JH collected the data, OL, ZN, RA provided the data analyses, RA is responsible for statistical analyses. All authors had input on interpretation and reporting of study findings.

KS wrote the first draft; all authors reviewed and edited the final version. All authors provided approval for the published version of this manuscript.

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Competing interests: None declared.

Provenance and peer review: Not commissioned; externally peer reviewed.

Ethics approval: The Ethics Committee of Motol University Hospital and St. Anne´s University Hospital approved the study.

Collaboration: Proposals for collaboration on specific data from the database or biospecimen (DNA, CSF, serum) are welcome. We have established a cohort which allows for integration of multiple clinical data with biomarkers and lifestyle factors. The details about the study are accessible on www.cbas.cz. We encourage collaborations with researchers from other cohort studies with similar aspects to increase sample size.

Data sharing: Data are available upon reasonable request**.** All proposals for specific analyses are reviewed by a scientific committee. Data ownership remains with the center that obtained

the data originally. Inquiries about the data sharing from the CBAS database, data re-use or biospecimen can be addressed to the corresponding author and/or the Principal Investigator through email: sheardova@fnusa.cz, jakub.hort@fnmotol.cz

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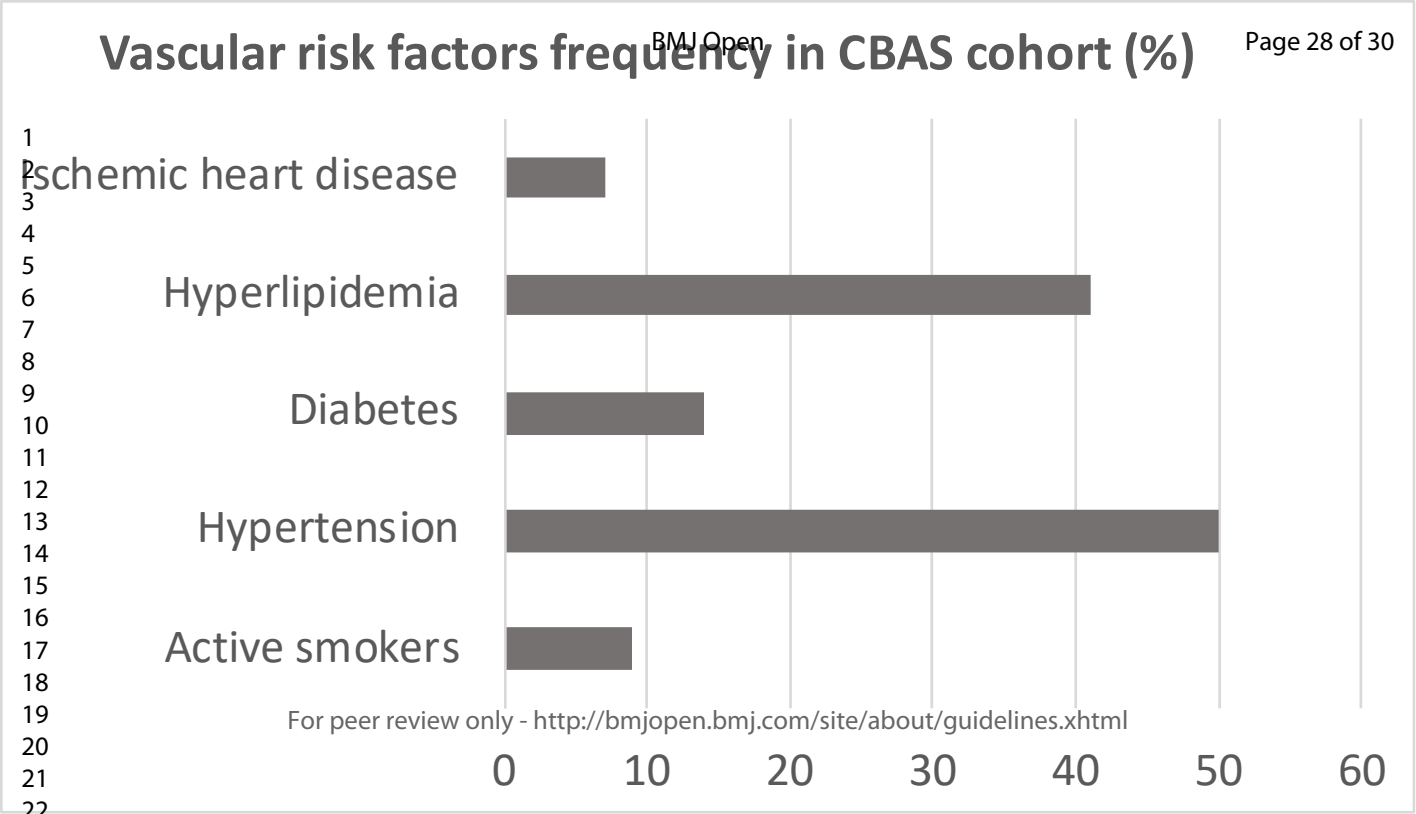
Figure legends:

Figure 1 The frequency of vascular risk factors in CBAS cohort



STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	4-8
Objectives	3	State specific objectives, including any prespecified hypotheses	7-8
Methods			
Study Design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8, 13-14
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	NA
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	NA
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	NA
		Case-control study—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-12

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-12
Bias	9	Describe any efforts to address potential sources of bias	17
Study Size	10	Explain how the study size was arrived at	9
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	NA
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	14, 17 NA NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9,13
		(b) Give reasons for non-participation at each stage	14
		(c) Consider use of a flow diagram	
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10,14
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	14
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	15-16
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key Results	18	Summarise key results with reference to study objectives	15-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

BMJ Open

Cohort Profile: "The Czech Brain Aging Study (CBAS) – prospective multicenter cohort study on risk and protective factors for dementia in the Czech Republic"

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Primary Subject Heading:	Epidemiology
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Keywords:	Dementia < NEUROLOGY, EPIDEMIOLOGY, MENTAL HEALTH

Cohort Profile: "The Czech Brain Aging Study (CBAS) – prospective multicenter cohort study on risk and protective factors for dementia in the Czech Republic"

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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+, 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 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 (CSF, amyloid PET) and spatial navigation are performed. Participants are 69.7±8.1 years old, have 14.6±3.3 years of education at baseline, and 59% are women. By the end of 2018, 31% finished 3 and more years of follow-up, 9% converted to dementia. APOE status is available from 95% of participants. Biological sample bank linked to CBAS database contains 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 on-going 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 at www.cbas.cz.

Key words: Dementia, epidemiology, mental health

STRENGHTS AND LIMITATIONS OF THE STUDY:

- CBAS is a prospective longitudinal study of cognitive and brain aging that combines prospective data on lifestyle, genetic, neuropsychological, social, physical and biological factors with neuropsychological and imaging data in the context of 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 generalizability, although universal health care 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 to 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 downwards 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 an 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. 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 neighboring countries such as Poland has been significantly lower compared to 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 health care delivery in the CR is a care delivery system that favors memory clinic visits from a wide spectrum of the patient population. In turn, prodromal stages of the disease are mostly handled by neurologists, whereas post-diagnostic 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 etiology 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 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 centers are harmonized in terms of neuropsychological battery, multimodality magnetic resonance imaging (MRI), 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 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 are 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 are: 1. Exploring epidemiological risk

factors for cognitive decline and dementia in the CR; 2. Evaluation of spatial navigation and other experimental neuropsychological tests as early markers of AD pathology; 3. Defining structural, metabolic and functional biomarkers of neurodegenerative diseases in older adults; and 4. Exploring non-pharmacological interventions in prevention of cognitive decline.

COHORT DESCRIPTION

Settings

CBAS is a prospective longitudinal memory clinic based multi-center study recruiting non-demented adults 55+ years of age. Both CBAS centers 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 exclusion criteria below) 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 categorized as subjective cognitive decline (SCD). Participants with objective cognitive decline are classified as mild cognitive impairment (MCI) based on 2011 NIA-AA guidelines by Albert and colleagues.[8] Cognitively healthy controls or normal controls (NC), 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. The Ethics Committees of Motol University Hospital and St. Anne´s University Hospital approved 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 enrollment 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 to national average reported in 2004.

Table 1. Basic characteristics of the CBAS cohort at baseline

	Total			SCD			MCI			NC		
	mean (SD) or ratio	median or %	Inter quartile range	mean (SD) or ratio	median or %	Inter quartile range	mean (SD) or ratio	median or %	Inter quartile range	mean (SD) or ratio	median or %	Inter quartile range
No. 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)	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

Notes: SD = standard deviation; GDS = Geriatric Depression Scale[9]

Apolipoprotein E4 (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+ living in the CR, 12% of whom are 80+ and 6% are 85+ 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 above, 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 origin, depression, history of stroke etc. and who signed informed consent. Dementia etiology (AD dementia, frontotemporal lobar degeneration, Parkinsonian syndromes, vascular disorders etc.) is diagnosed according to established guidelines.[10] 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 co-morbidity.

Methods

At each visit, all study participants undergo a standard set of procedures. Neurological and comprehensive neuropsychology examination including Uniform Data Set (UDS) battery is administered;[11, 12] laboratory and vital functions assessments are also performed. Socio-demographic, personal, pharmacological and family history data are collected. Participants

and their informants complete multiple questionnaires about cognitive complaints and lifestyle factors. 1.5T or 3T MRI scans 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 analyzed in all patients to obtain measures of regional cortical thickness and subcortical volumes cross-sectionally and longitudinally using Freesurfer image analysis suite (v5.3; http://surfer.nmr.mgh.harvard.edu/). The details of Freesurfer image processing have been published elsewhere,[13-15] including previous studies by our group.[16, 17] 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.[18] 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.

Table 2. The CBAS Procedures

Frequency	Procedure	Specification
Annually	Clinical exam	Standard complex neurology examination
Annually	Standard neuropsychology	**Uniform Data Set**[11, 12]: Mini-Mental State Examination, Digit Span Forward and Backward, Digit Symbol, Trail Making Test A and B, Animal list generation, Vegetable list generation, Boston Naming Test (30 odd items), Logical Memory, Story A **Premorbid ability estimation**: National Adult Reading Test[19] **Memory assessment:** Enhanced cued recall test,[20] Rey Auditory Verbal Learning Test,[21] Brief Visuospatial Memory Test–Revised,[22] Rey-Osterrieth Complex Figure Test – (ROCFT) recall[23] **Executive functions**: Prague Stroop test,[24] Similarities (WAIS-R)[25], Controlled Oral Word Association Test[26] **Visuoconstruction**: Clock Test,[27] ROCFT copy[23] **Functional scales**: Clinical Dementia Rating scale,[28] Functional assessment questionnaire[29] **Symptoms of anxiety and depression**: Geriatric Depression Scale (15 items version),[9] Beck Anxiety Inventory[30]

Annually	Laboratory	Fasting glucose, lipid profile, homocysteine, vitamin B12, thyroid hormones, folic acid, renal and liver function, C-reactive protein, glycosylated hemoglobin
Annually	Vital functions	blood pressure, pulse frequency, waist/hips ratio, BMI
Annually	Socio- economic data	Marital status, Type of living, Current occupation
Annually	Questionnaires	Subjective cognitive complaints (QPC),[31] physical/mental activity at midlife and currently, Becke's Habitual Physical Activity[32], Epworth Sleepiness Scale,[33] Falls Self-Efficacy Scale – International[34]
Biannually	MRI	1.5T protocol: plane localizer; standard clinical T2; T1 3-dimensional isometric magnetization-prepared rapid gradient echo(MPRAGE) with isometric voxel; fluid-attenuated inversion recovery(FLAIR); T2*; echoplanar imaging for diffusion tensor imaging with 32directions.3T protocol: plane localizer; standard clinical T1 and T2; T1 3-dimensional isometric magnetization-prepared rapid gradient echo (MPRAGE) with isometric voxel; echoplanar imaging for diffusion tensor imaging with 64 directions; fluid-attenuated inversion recovery (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, laterality
At baseline all Optional	Genotyping	APOE 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[35, 36, 37]	hidden goal task, simple navigation task, path integration task, Y-maze assessment, intersections task, sea hero quest, spatial tasks in virtual reality/augmented virtual reality
Prague cohort optional	Experimental neuropsychology	Facial emotion recognition,[38, 39] Famous faces identification,[39] FNAME 12 items version,[40] Memory binding test,[41] spatial pattern separation task[42] In house developed tests: Famous landmarks identification,[43] episodic-like memory test,[44] Arena Perspective Taking Task[45]
Brno cohort All at baseline	Specific questionnaires	Spiritual well-being questionnaire (SHALOM),[46] Operationalized Psychodynamic Diagnostics OPD-2 (OPD working group),[47] early life trauma assessment

The CBAS is complemented by a biological sample bank linked to data from the CBAS and "CBAS Plus" cohorts. The CSF collection and storage are carried out after signing an informed consent in accordance with the ethical guidelines in the CR and good clinical practice, and according to the widely recognized consensus protocol for the standardization of cerebrospinal fluid collection and biobanking.[48] Eighteen aliquots of 0.2ml 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.[49] The characteristics of the biobank as of December 2018 are listed in table 3.

Table 3. Biobank characteristics

	Aliquots per patient stored at -80C	No. of participants
CSF	18x0.2ml	75 in Brno/350 in Prague
Serum	5-9x0.5ml	145 in Brno/350 in Prague
DNA	concentration >100 ng/µl	95% of all participants

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 3 visits are followed 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 etiology is based on biomarkers.[8, 10]

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 3 full yearly evaluations (baseline + 2 follow up visits) with at least 2 brain MRI sessions. Additionally, 9% of all participants converted to dementia at some timepoint within their follow-up and were no longer followed, and 16% of the participants were lost to follow-up for various reasons (loss of interest, newly acquired MRI intolerance, worsening health condition, change of residence address not allowing invitation for follow up, etc.). 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 participants to begin with longitudinal data analyses which will contribute significantly to the fulfillment of most of the study aims.

Patient and public involvement

Patient involvement was crucial in questionnaire implementation. Initial versions of 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 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[43] or the Subjective Spatial Memory Complaints Questionnaire,[50] 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.

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, CBAS webpage, etc. We also closely cooperate with Czech Alzheimer Association (CAA) connecting dementia specialists with patients and their caregivers. Many CAA 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[35, 36] (for details see table 2). Outcomes of this comprehensive examination have been compared with results of structural brain MRI and genetic and laboratory assessment. Our cross-sectional studies using clinically and biomarker-defined individuals with AD[51] 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[52, 53] and may be useful for early and differential diagnosis of AD, or for evaluating the effect of therapies.[37, 54] Longitudinal study will aim to provide evidence for this notion. It should be noted that other co-pathologies may negatively impact on spatial navigation performance in individuals with AD.[55, 56]

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, i.e. the structures that are impaired very early in AD[16, 18, 52] and that it can be influenced by genetic background[57, 58] and cardiovascular risk factors.[59]

Experimental neuropsychology

We have shown that our "in-house" developed Famous Landmarks Identification Test, created with the help from our participants, could be useful in recognizing early stages of AD.[43] 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.[60]

Lifestyle factors and AD

We have recently completed the first longitudinal MRI analysis from CBAS[61] 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 behavioral symptoms. The manuscript is being prepared for publication. Previous studies have included examinations of cholesterol[62] and blood glucose[63] 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[64] 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.

STRENGHTS 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, 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,[65] 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 cannot compete with a population-based recruitment. Although it is also of note that due to the nature of health care 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. 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.[66] However, although the average age for patients with MCI is substantially lower than the UK-based Cognitive Function & Ageing Studies, it is roughly similar to studies from Italy, Spain, Australia, and studies conducted in Asia.[67] 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 aging in the Czech Republic 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.

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FOOTNOTES:

Patient consent for publication: Not required

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Collaboration: Proposals for collaboration on specific data from the database or biospecimen (DNA, CSF, serum) are welcome. We have established a cohort which allows for integration of multiple clinical data with biomarkers and lifestyle factors. The details about the study are

accessible on www.cbas.cz. We encourage collaborations with researchers from other cohort studies with similar aspects to increase sample size.

Data sharing: Data are available upon reasonable request**.** All proposals for specific analyses are reviewed by a scientific committee. Data ownership remains with the center that obtained the data originally. Inquiries about the data sharing from the CBAS database, data re-use or biospecimen can be addressed to the corresponding author and/or the Principal Investigator through email: sheardova@fnusa.cz, jakub.hort@fnmotol.cz

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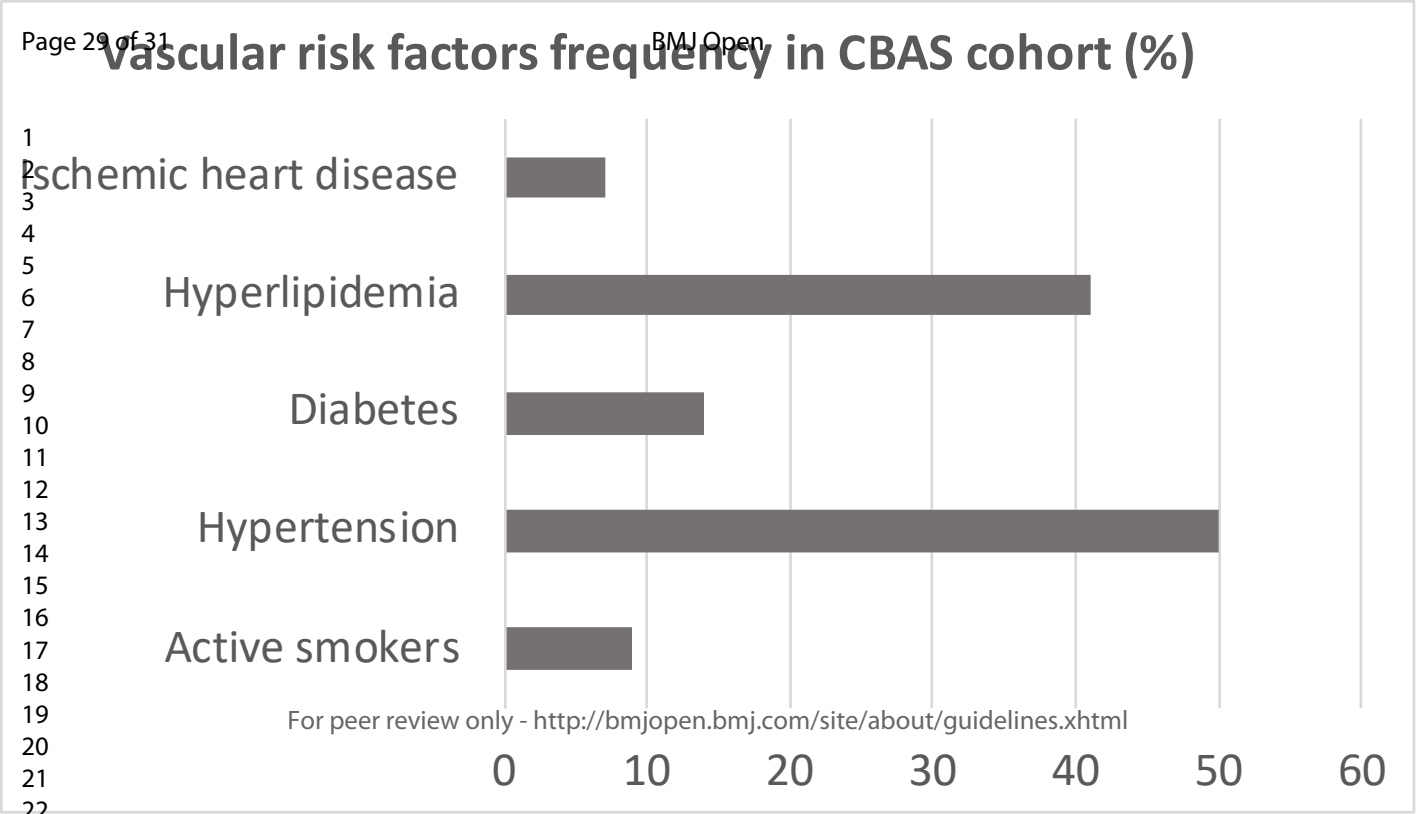
Figure legends:

Figure 1 The frequency of vascular risk factors in CBAS cohort



STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	4-8
Objectives	3	State specific objectives, including any prespecified hypotheses	7-8
Methods			
Study Design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8, 13-14
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	NA
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	NA
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	NA
		Case-control study—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-12

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-12
Bias	9	Describe any efforts to address potential sources of bias	17
Study Size	10	Explain how the study size was arrived at	9
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	NA
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	14, 17
		Case-control study—If applicable, explain how matching of cases and controls was addressed	NA
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9,13
		(b) Give reasons for non-participation at each stage	14
		(c) Consider use of a flow diagram	
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10,14
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	14
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	15-16
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key Results	18	Summarise key results with reference to study objectives	15-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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BMJ Open

Cohort Profile: "The Czech Brain Aging Study (CBAS) – prospective multicenter cohort study on risk and protective factors for dementia in the Czech Republic"

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Mental health, Public health, Neurology
Keywords:	Dementia < NEUROLOGY, EPIDEMIOLOGY, MENTAL HEALTH

Cohort Profile: "The Czech Brain Aging Study (CBAS) – prospective multicenter cohort study on risk and protective factors for dementia in the Czech Republic"

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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+, 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 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 (CSF, amyloid PET) and spatial navigation are performed. Participants are 69.7±8.1 years old, have 14.6±3.3 years of education at baseline, and 59% are women. By the end of 2018, 31% finished 3 and more years of follow-up, 9% converted to dementia. APOE status is available from 95% of participants. Biological sample bank linked to CBAS database contains 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 on-going 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 at www.cbas.cz.

Key words: Dementia, epidemiology, mental health

STRENGHTS AND LIMITATIONS OF THE STUDY:

- CBAS is a prospective longitudinal study of cognitive and brain aging that combines prospective data on lifestyle, genetic, neuropsychological, social, physical and biological factors with neuropsychological and imaging data in the context of 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 generalizability, although universal health care 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 to 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 downwards 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 an 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. 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 neighboring countries such as Poland has been significantly lower compared to 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 health care delivery in the CR is a care delivery system that favors memory clinic visits from a wide spectrum of the patient population. In turn, prodromal stages of the disease are mostly handled by neurologists, whereas post-diagnostic 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 etiology 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 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 centers are harmonized in terms of neuropsychological battery, multimodality magnetic resonance imaging (MRI), 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 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 are 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 are: 1. Exploring epidemiological risk

factors for cognitive decline and dementia in the CR; 2. Evaluation of spatial navigation and other experimental neuropsychological tests as early markers of AD pathology; 3. Defining structural, metabolic and functional biomarkers of neurodegenerative diseases in older adults; and 4. Exploring non-pharmacological interventions in prevention of cognitive decline.

COHORT DESCRIPTION

Settings

CBAS is a prospective longitudinal memory clinic based multi-center study recruiting non-demented adults 55+ years of age. Both CBAS centers 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 exclusion criteria below) 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 categorized as subjective cognitive decline (SCD). Participants with objective cognitive decline are classified as mild cognitive impairment (MCI) based on 2011 NIA-AA guidelines by Albert and colleagues.[8] Cognitively healthy controls or normal controls (NC), 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. The Ethics Committees of Motol University Hospital and St. Anne´s University Hospital approved 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 enrollment 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 to national average reported in 2004.

Table 1. Basic characteristics of the CBAS cohort at baseline

	Total			SCD			MCI			NC		
	mean (SD) or ratio	median or %	Inter quartile range	mean (SD) or ratio	median or %	Inter quartile range	mean (SD) or ratio	median or %	Inter quartile range	mean (SD) or ratio	median or %	Inter quartile range
No. 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)	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

Notes: SD = standard deviation; GDS = Geriatric Depression Scale[9]

Apolipoprotein E4 (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+ living in the CR, 12% of whom are 80+ and 6% are 85+ 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 above, 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 origin, depression, history of stroke etc. and who signed informed consent. Dementia etiology (AD dementia, frontotemporal lobar degeneration, Parkinsonian syndromes, vascular disorders etc.) is diagnosed according to established guidelines.[10] 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 co-morbidity.

Methods

At each visit, all study participants undergo a standard set of procedures. Neurological and comprehensive neuropsychology examination including Uniform Data Set (UDS) battery is administered;[11, 12] laboratory and vital functions assessments are also performed. Socio-demographic, personal, pharmacological and family history data are collected. Participants

and their informants complete multiple questionnaires about cognitive complaints and lifestyle factors. 1.5T or 3T MRI scans 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 analyzed in all patients to obtain measures of regional cortical thickness and subcortical volumes cross-sectionally and longitudinally using Freesurfer image analysis suite (v5.3; http://surfer.nmr.mgh.harvard.edu/). The details of Freesurfer image processing have been published elsewhere,[13-15] including previous studies by our group.[16, 17] 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.[18] 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.

Table 2. The CBAS Procedures

Frequency	Procedure	Specification
Annually	Clinical exam	Standard complex neurology examination
Annually	Standard neuropsychology	**Uniform Data Set**[11, 12]: Mini-Mental State Examination, Digit Span Forward and Backward, Digit Symbol, Trail Making Test A and B, Animal list generation, Vegetable list generation, Boston Naming Test (30 odd items), Logical Memory, Story A **Premorbid ability estimation**: National Adult Reading Test[19] **Memory assessment:** Enhanced cued recall test,[20] Rey Auditory Verbal Learning Test,[21] Brief Visuospatial Memory Test–Revised,[22] Rey-Osterrieth Complex Figure Test – (ROCFT) recall[23] **Executive functions**: Prague Stroop test,[24] Similarities (WAIS-R)[25], Controlled Oral Word Association Test[26] **Visuoconstruction**: Clock Test,[27] ROCFT copy[23] **Functional scales**: Clinical Dementia Rating scale,[28] Functional assessment questionnaire[29] **Symptoms of anxiety and depression**: Geriatric Depression Scale (15 items version),[9] Beck Anxiety Inventory[30]

Annually	Laboratory	Fasting glucose, lipid profile, homocysteine, vitamin B12, thyroid hormones, folic acid, renal and liver function, C-reactive protein, glycosylated hemoglobin
Annually	Vital functions	blood pressure, pulse frequency, waist/hips ratio, BMI
Annually	Socio- economic data	Marital status, Type of living, Current occupation
Annually	Questionnaires	Subjective cognitive complaints (QPC),[31] physical/mental activity at midlife and currently, Becke's Habitual Physical Activity[32], Epworth Sleepiness Scale,[33] Falls Self-Efficacy Scale – International[34]
Biannually	MRI	1.5T protocol: plane localizer; standard clinical T2; T1 3-dimensional isometric magnetization-prepared rapid gradient echo(MPRAGE) with isometric voxel; fluid-attenuated inversion recovery(FLAIR); T2*; echoplanar imaging for diffusion tensor imaging with 32directions.3T protocol: plane localizer; standard clinical T1 and T2; T1 3-dimensional isometric magnetization-prepared rapid gradient echo (MPRAGE) with isometric voxel; echoplanar imaging for diffusion tensor imaging with 64 directions; fluid-attenuated inversion recovery (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, laterality
At baseline all Optional	Genotyping	APOE 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[35, 36, 37]	hidden goal task, simple navigation task, path integration task, Y-maze assessment, intersections task, sea hero quest, spatial tasks in virtual reality/augmented virtual reality
Prague cohort optional	Experimental neuropsychology	Facial emotion recognition,[38, 39] Famous faces identification,[39] FNAME 12 items version,[40] Memory binding test,[41] spatial pattern separation task[42] In house developed tests: Famous landmarks identification,[43] episodic-like memory test,[44] Arena Perspective Taking Task[45]
Brno cohort All at baseline	Specific questionnaires	Spiritual well-being questionnaire (SHALOM),[46] Operationalized Psychodynamic Diagnostics OPD-2 (OPD working group),[47] early life trauma assessment

The CBAS is complemented by a biological sample bank linked to data from the CBAS and "CBAS Plus" cohorts. The CSF collection and storage are carried out after signing an informed consent in accordance with the ethical guidelines in the CR and good clinical practice, and according to the widely recognized consensus protocol for the standardization of cerebrospinal fluid collection and biobanking.[48] Eighteen aliquots of 0.2ml 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.[49] The characteristics of the biobank as of December 2018 are listed in table 3.

Table 3. Biobank characteristics

	Aliquots per patient stored at -80C	No. of participants
CSF	18x0.2ml	75 in Brno/350 in Prague
Serum	5-9x0.5ml	145 in Brno/350 in Prague
DNA	concentration >100 ng/µl	95% of all participants

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 3 visits are followed 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 etiology is based on biomarkers.[8, 10]

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 3 full yearly evaluations (baseline + 2 follow up visits) with at least 2 brain MRI sessions. Additionally, 9% of all participants converted to dementia at some timepoint within their follow-up and were no longer followed, and 16% of the participants were lost to follow-up for various reasons (loss of interest, newly acquired MRI intolerance, worsening health condition, change of residence address not allowing invitation for follow up, etc.). 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 participants to begin with longitudinal data analyses which will contribute significantly to the fulfillment of most of the study aims.

Patient and public involvement

Patient involvement was crucial in questionnaire implementation. Initial versions of 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 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[43] or the Subjective Spatial Memory Complaints Questionnaire,[50] 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.

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, CBAS webpage, etc. We also closely cooperate with Czech Alzheimer Association (CAA) connecting dementia specialists with patients and their caregivers. Many CAA 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[35, 36] (for details see table 2). Outcomes of this comprehensive examination have been compared with results of structural brain MRI and genetic and laboratory assessment. Our cross-sectional studies using clinically and biomarker-defined individuals with AD[51] 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[52, 53] and may be useful for early and differential diagnosis of AD, or for evaluating the effect of therapies.[37, 54] Longitudinal study will aim to provide evidence for this notion. It should be noted that other co-pathologies may negatively impact on spatial navigation performance in individuals with AD.[55, 56]

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, i.e. the structures that are impaired very early in AD[16, 18, 52] and that it can be influenced by genetic background[57, 58] and cardiovascular risk factors.[59]

Experimental neuropsychology

We have shown that our "in-house" developed Famous Landmarks Identification Test, created with the help from our participants, could be useful in recognizing early stages of AD.[43] 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.[60]

Lifestyle factors and AD

We have recently completed the first longitudinal MRI analysis from CBAS[61] 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 behavioral symptoms. The manuscript is being prepared for publication. Previous studies have included examinations of cholesterol[62] and blood glucose[63] 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[64] 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.

STRENGHTS 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, 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,[65] 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 doesn't create population representation. Although it is also of note that due to the nature of health care 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 health care 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.[66] However, although the average age for patients with MCI is substantially lower than the UK-based Cognitive Function & Ageing Studies, it is roughly similar to studies from Italy, Spain, Australia, and studies conducted in Asia.[67] 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 aging in the Czech Republic 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.

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FOOTNOTES:

Patient consent for publication: Not required

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

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Competing interests: None declared.

Provenance and peer review: Not commissioned; externally peer reviewed.

Ethics approval: The Ethics Committee of Motol University Hospital and St. Anne´s University Hospital approved the study.

Collaboration: Proposals for collaboration on specific data from the database or biospecimen (DNA, CSF, serum) are welcome. We have established a cohort which allows for integration of multiple clinical data with biomarkers and lifestyle factors. The details about the study are

accessible on www.cbas.cz. We encourage collaborations with researchers from other cohort studies with similar aspects to increase sample size.

Data sharing: Data are available upon reasonable request**.** All proposals for specific analyses are reviewed by a scientific committee. Data ownership remains with the center that obtained the data originally. Inquiries about the data sharing from the CBAS database, data re-use or biospecimen can be addressed to the corresponding author and/or the Principal Investigator through email: sheardova@fnusa.cz, jakub.hort@fnmotol.cz

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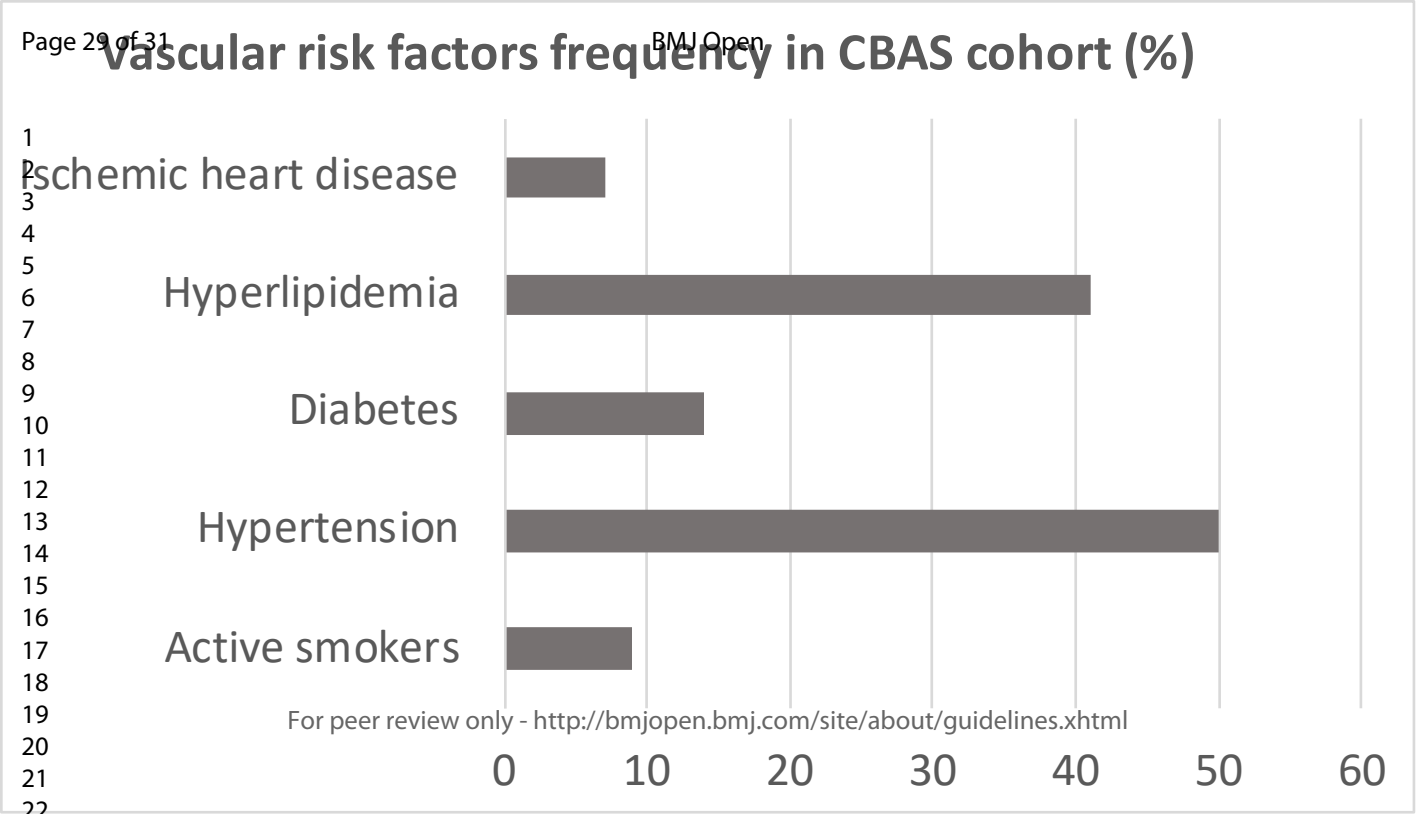
Figure legends:

Figure 1 The frequency of vascular risk factors in CBAS cohort



STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	4-8
Objectives	3	State specific objectives, including any prespecified hypotheses	7-8
Methods			
Study Design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8, 13-14
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	NA
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	NA
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	NA
		Case-control study—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-12

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-12
Bias	9	Describe any efforts to address potential sources of bias	17
Study Size	10	Explain how the study size was arrived at	9
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	NA
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	14, 17
		Case-control study—If applicable, explain how matching of cases and controls was addressed	NA
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9,13
		(b) Give reasons for non-participation at each stage	14
		(c) Consider use of a flow diagram	
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10,14
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	14
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	15-16
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key Results	18	Summarise key results with reference to study objectives	15-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.