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Brain health over the life-course

Habilitation thesis

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Abstract

Part 1: Epidemiology of brain disorders in the Czech Republic
Aims: To examine prevalence of mental disorders and associated treatment gap; find out whether occurrence of cognitive impairment and depressive symptoms changed over time in older adults.
Methods: Data comes from CZEch Mental health Study and Survey on Health, Ageing and Retirement in Europe (SHARE). Mental disorders were assessed by a diagnostic interview; cognitive impairment was defined with an algorithm based on measures of verbal fluency, immediate recall, delayed recall and temporal orientation; depressive symptoms were assessed by EURO-D scale.
Results: The prevalence of alcohol use disorders is 11%, followed by anxiety disorders (7%), affective disorders (5.5%), substance use disorders (3%) and psychotic disorders (1.5%). Treatment gap ranged from 61% for affective disorders to 93% for alcohol use disorders. Between 2006/2007 and 2015, the age-specific prevalence of cognitive impairment and depressive symptoms decreased in older adults.

Part 2: Depressive symptoms and cognitive health of older Europeans
Aims: To determine how European regions differ in depressive symptoms, cognitive performance and rate of cognitive decline and study whether living situation and comorbid diabetes mellitus influences the management of dementia.
Methods: Data comes from SHARE and the Swedish Dementia Registry. Depressive symptoms were assessed by EURO-D scale; cognition was defined by measures of verbal fluency, immediate recall and delayed recall.
Results: The prevalence of depressive symptoms was highest in Southern Europe (35%), followed by Central and Eastern Europe (32%), Western Europe (26%) and the lowest in Scandinavia (17%). Participants from Scandinavia reached the highest scores in cognitive tests, followed by Western Europe, Central and Eastern Europe and Southern Europe. Individuals in Scandinavia had also the highest rate of cognitive decline. Amongst patients with Alzheimer´s disease, living alone was associated with lower odds of receiving diagnostic examinations and prescription of anti-dementia drugs. Comorbid diabetes mellitus was also associated with lower odds of anti-dementia drugs.

Part 3: Life-course perspective on brain health
Aims: To find out whether subclinical cardiac dysfunction in young adulthood and atherosclerosis are associated with MRI markers of brain health in mid-life and examine the association of childhood socioeconomic position with cognition and depressive symptoms in later adulthood.
Methods: Data comes from Coronary Artery Risk Development In Young Adults, SHARE and Health, Alcohol and Psychological factors In Eastern Europe. Markers of brain health were assessed by MRI, cognition was defined using measures of verbal fluency, immediate recall and delayed recall; depressive symptoms were measured with CES-D scale.
Results: Higher left atrial volume in young adulthood is associated with lower white matter fractional anisotropy in mid-life. Higher carotid intima-media thickness is associated with lower brain perfusion in middle-aged adults. Childhood socioeconomic hardship is related to a lower level of cognitive performance and depressive symptoms in later adulthood, but not to the rate of cognitive decline.

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List of abbreviations

AD: Alzheimer´s disease
ATC: Anatomical Therapeutical and Chemical
BMI: body mass index
CAPI: computer-assisted personal interview
CARDIA: Coronary Artery Risk Development in Young Adults
CEE: Central and Eastern Europe
CES-D: Center for Epidemiological Studies – Depression
CI: confidence interval
cIMT: carotid intima-media thickness
CT: computerized tomography
CVRF: cardiovascular risk factor
CZEMS: CZEch Mental health Study
DM: diabetes mellitus
HAPIEE: Health, Alcohol and Psychosocial factors In Eastern Europe
IADL: instrumental activity of daily living
ICD: International Classification of Diseases
LP: lumbar puncture
M.I.N.I.: Mini International Neuropsychiatric Interview
MMSE: Mini Mental State Examination
MRI: Magnetic Resonance Imaging
OR: odds ratio
PAPI: paper and pencil interview
SD: standard deviation
SELFI: Self-Identification as Having a Mental Illness
SEM: structural equation modelling
SEP: socioeconomic position
SHARE: Survey of Health, Ageing and Retirement in Europe
SveDem: Swedish Dementia Registry
WHO: World Health Organization
WHODAS: World Health Organization Disability Assessment Scale

Content

1 Introduction

1.1 Brain disorders and brain health

Disorders of the brain, previously marginalized and stigmatized, are receiving growing global attention in the 21st century[1, 2]. Mental and neurological disorders deserve to be studied and conceptualized together due to their frequent co-occurrence and shared underlying mechanisms[3]. They are also often referred to as "mental, neurological and substance use disorders", "neuropsychiatric disorders" or simply "brain disorders" and comprise of hundreds of specific diagnoses[3, 4]. The increased focus of researchers and clinicians on disorders of the brain likely stems from the fact that they are much more frequent than admitted in the past and cause a greater burden to society than previously expected[3]. Impairments in psychosocial functioning due to brain disorders are tremendous and brain disorders are even the leading cause of years lost to disability from all diseases[5]. Therefore, brain disorders are exceptionally costly[6], in particular due to substantial indirect costs related to loss of productivity of the affected individuals and their caregivers[3].

The term "disorders of the brain" or "brain disorders" is used in this thesis, which deals specifically with affective and cognitive disorders and to a smaller extent also substance use, anxiety and psychotic disorders. On the opposite end of the spectrum, the concept of brain health is emerging. As health is much more than the absence of diseases[7], so does brain health go beyond the lack of brain disorders. Some attempts have been made to operationalize brain health. For example, the Center for Disease Control and Prevention in the United States of America states that a healthy brain is able to perform mental processes that encompass cognition, such as learning, judging, remembering and using language[8]. This definition is appropriate for the context of cognitive disorders of the ageing populations[8], however, it lacks recognition of the emotional brain health and largely a component of overall mental health. As defined by the World Health Organization (WHO), mental health can be characterized as a state of well-being, in which an individual can realize their potential, can cope with normal stresses of life, can work productively and fruitfully, and is able to make a contribution to their community[9].

1.2 Challenges of the ageing population

Brain disorders are in nature multifactorial in etiology, with biopsychosocial components interacting as risk and protective factors for their pathogenesis. As such, most brain disorders are not inevitable

and we can modify their risks. Brain health should be the desired outcome of strategies aiming to reduce the occurrence of brain disorders. Maintaining brain health is a life-course process that has specific challenges across each stage of life. Given the continuously increasing life expectancy and the rising share of older adults in the populations worldwide, brain disorders of the aging population are considered of utmost importance. One of the major concerns for brain health of older adults is their cognitive health, which largely determines their independence. Secondly, depression occurring in late life is another cause of disability in older adults and is associated with cognitive and physical decline, poor quality of life as well as excess mortality[10]. While some studies point out to a high burden of depression in older adults, other authors contradict them by suggesting that the occurrence of depression declines with increasing age[11]. Such conflicting findings may be a combination of survival bias and use of inadequate measurement tools for detection of depression in older adults[11].

Progressive decline in cognitive functions that interferes with daily functioning characterizes the syndrome of dementia[12]. Alzheimer´s disease (AD) is considered the most common type, followed by vascular dementia[12]. The overlap between vascular changes and AD pathology is, however, substantial and mixed dementia is by some authors considered as the most common dementia type, in particular among the oldest individuals[13, 14]. A strong link between risk of dementia and cardiovascular health is well known[15]. The association of cardiovascular risk factors (CVRFs), including hypertension, diabetes mellitus (DM), physical inactivity, smoking and hypercholesterolemia, was discovered almost two decades ago and since then replicated in multiple epidemiological studies[16-20]. As there is currently no disease-modifying treatment for dementia, major hopes have been raised for its prevention, in particular through reduction of CVRFs[12].

Dementia is diagnosed at the average age of 80 years[21-23], but has a long pre-clinical period. Population-based studies indicate that individuals aged already 50 years old may have established functional or structural changes of the brain, such as white matter injury or decreased brain perfusion[24-26], likely due to previous long term exposure to CVRFs[24]. These pathologies may accumulate over time and form a functional and structural basis for the development of dementia. The pathophysiological foundation for the aforementioned observations could be atherosclerosis. In addition, intact cardiac function is needed to maintain cerebral perfusion in order to preserve brain health[27]. Mounting evidence from general and patient populations indicates that individuals with heart failure have a greater risk of dementia[27-30], but the effect of cardiac function on the brain is not

limited only to patients with advanced heart failure. Even subtle cardiac dysfunction is associated with lower markers of neurodegenerative and cerebrovascular pathologies[31-35]. It may be hypothesized that subclinical cardiac dysfunction, which occurs even in some sub-groups of young adults[36, 37], may contribute to brain disorders as early as in mid-life.

1.3 Treatment gap

Compared to other diseases, the direct costs of health care for brain disorders are substantially lower[3]. In fact, a major proportion of individuals with brain disorders do not receive any health care at all. The disparity between the prevalence of the disease and the proportion of affected individuals that receive treatment has been referred to as "treatment gap"[38]. Globally, the overall treatment gap for brain disorders likely exceeds 50% and rises to 90% in low and middle income countries[38]. Causes for the treatment gap include a combination of under-recognition of symptoms, lack of insight of the affected individuals, under-utilization of heath care, under-treatment of individuals who have contact with services, non-adherence to treatment as well as a lack of human and other resources[3]. Thus, multiple causes operate on the level of affected individuals, their families, health care and social care services as well as milieu in the society[39, 40].

Higher age likely contributes to the major treatment gap for brain disorders. Several reasons may explain this. In the context of depression in older adults, symptoms in old age differ from those experienced by younger individuals; for example, depression without sadness is common in older age[41]. Further, frequent comorbidities are barriers to the detection of depression. Fatigue, cognitive impairment, apathy and other signs of depression of older adults may be perceived as signs of somatic diseases[41]. Older adults are also less likely than younger adults to recognize signs of depression and to perceive a need to seek treatment[42], mostly because they wish to deal with their problems on their own[43]. Societal stigma towards brain disorders may be a barrier to utilization of services[44]. In addition, a negative approach to old age may cause under-prioritization of older adults in the health care system[45].

The structure of family and living situation likely affects the utilization of services as well as diagnostic and therapeutic decisions by physicians. It is well established that individuals with an advantagous family environment access somatic health care more frequently[46], however, the situation surrounding care for brain disorders is rather controversial. Families and close caregivers

sharing a household with affected individuals may enable better access to services in some cases, but families can be also a source of stress and barriers to health care, in particular concerning stigmatized mental disorders[47]. Cardiovascular and other comorbidities may be other reasons for the undertreatment of brain disorders, due to brain disorders competing for prioritization and investment amongst a vast range of comorbidities. Concerns about drug interaction may also play a major role in limiting treatment[48]. Overall, the large treatment gap for brain disorders may contribute to unfavourable outcomes of the affected individuals, and minimizing the gap remains a global public health priority[38].

1.4 Geographical inequalities

Brain disorders are not distributed equally across populations. For example, the prevalence of major depression is estimated to range between 2% and 8% in different European countries[49]. Some studies suggested a higher burden of depression and cognitive disorders in older adults residing in countries situated in Southern as well as Central and Eastern Europe (CEE), in comparison to Western Europe and Scandinavia[50-56]. Just as the occurrence of brain disorders in the world is unequal, so is the representation of epidemiological evidence. The region of CEE is an example of a wide geographical area with relatively little information on brain disorders[57]. CEE belongs to the regions with the highest estimated level of disability and mortality rates due to mental disorders in the world, however, precise data from specific countries are mostly lacking[5].

The absence of epidemiological data from CEE was apparent in several large international projects. For example, in a review published in 2016 that summarized evidence on declining incidence of dementia in Western Europe, Wu et al explicitly stated that no data from CEE countries is available[58]. No CEE country has been added into the 2017 review, where changes in eight countries were discussed[59]. In a critical appraisal of 27 studies on epidemiology of mental disorders in Europe, there was insufficient evidence from CEE[60] and no country from CEE is represented in a more recent review[3]. The large gap between the population health of the "West" and the "East" is well known[61, 62]. While cardiovascular morbidity and mortality have been declining since the 1970s in Western Europe, these rates have been increasing in CEE during the second half of the 20th century[61, 62]. These unfavourable trends have been attributed to socioeconomic disruptions at the national levels, leading to excessive alcohol consumption, poor nutrition, low physical activity, material hardship and

psychosocial distress[61-65]. These societal adversities likely contributed to a major burden of brain disorders in the populations of CEE.

Similar to many other CEE countries, the Czech Republic has gone through rapid social and economic transitions towards a westernized society following the end of communist rule in 1989. Recent studies suggest major improvements in the control of cardiovascular risk factors and declining mortality from ischemic heart disease and stroke[66-68]. It is likely that these positive changes are mirrored in improved brain health of the population. After many years of neglecting the burden of brain disorders in the Czech Republic, the Czech government has launched a reform that aims to modernize inefficient and outdated care, which has traditionally relied on institutionalized care in large hospitals. The lack of reliable epidemiological data about brain disorders in the Czech Republic is, however, an obstacle for planning and evaluating community-based services.

1.5 Roots in childhood socioeconomic position

It is well established that brain disorders which manifest in later adulthood do not emerge without reason, but rather follow exposures to a number of adverse factors over the life-course. Some brain disorders may have their roots in adverse conditions that individuals faced while growing up[69-76]. The most common childhood adversity is socioeconomic hardship[77], which may negatively impact various biological systems[78], leading to impairments in the autonomic nervous system, emotional reactivity, motivation and affect. This may make the individuals utilize negative emotional schemas, which in turn poses a risk for the development of depression[79-82]. Socioeconomic position (SEP) in childhood, often operationalized by educational attainment of parents or housing conditions[83, 84], is also a major determinant of educational attainment and development of cognitive skills, which may buffer against stressful life events[85] and protect against depression as well as cognitive decline[78]. Three conceptual frameworks may explain the relationship between childhood SEP and cognition.

First, childhood SEP may influence cognitive abilities in later adulthood by shaping the development of the brain so it tolerates more pathology before it reaches the threshold for manifestation of cognitive impairment[86]. Using the construct of passive cognitive reserve, this framework suggests that individuals exposed to socioeconomic hardship in childhood will have a lower level of cognitive performance in old age. Second, childhood SEP may also contribute to the foundation of an active cognitive reserve, possibly facilitating the use of pre-existing processes or compensatory

mechanisms in coping with brain pathology[86]. The second mechanism thus suggests that socioeconomic hardship in childhood would be associated with a higher rate of cognitive decline. Third, socioeconomic adversities in childhood might set an individual on a pathway towards risky and unhealthy behaviour and thus exposure to social and cardiovascular risks, which are all associated with an increased risk of cognitive impairment[87]. The third mechanism thus proposes that childhood SEP is not associated with cognition, after the adjustment for these clinical and social risk factors. Understanding how childhood SEP may lead to brain disorders in later life could help to target strategies to protect brain health over the life-course.

1.6 About this thesis

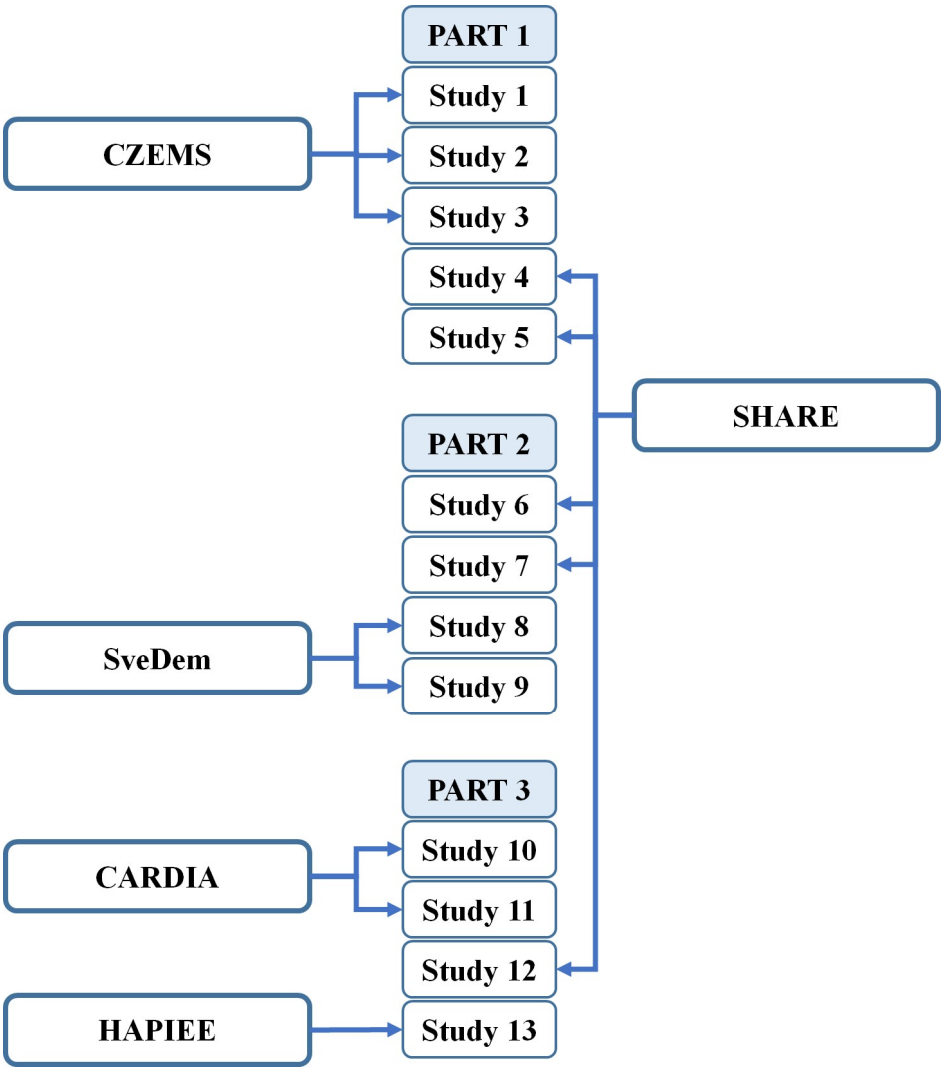

Figure 1 Structure of the thesis

CARDIA, Coronary Artery Risk Development in Young Adults; CZEMS, CZEch Mental health Study; HAPIEE, Health, Alcohol and Psychosocial factors In Eastern Europe; SHARE, Survey on Health, Ageing and Retirement in Europe; SveDem, Swedish Dementia Registry

This thesis is a commented set of 13 articles that address several gaps in knowledge in the context of brain health over the life-course of different populations. It consists of three parts (Figure 1). Part 1 is entitled "Epidemiology of mental disorders in the Czech Republic" and consists of five articles (Study 1-5). They concern the burden of mental disorders in the general population of community-dwelling adults residing in the Czech Republic as well as trends in the occurrence of depressive symptoms and cognitive impairment in older adults.

The theme of Part 2 is "Depressive symptoms and cognitive health in older Europeans". It consists of four articles (Study 6-9) that address inequalities in the distribution of symptoms of brain ill-health as well as utilization of services in adults older than 65 years residing in different European countries. Part 3 is entitled "Life-course perspective on brain health" and consists of four articles (Study 10-13). Focusing on the outcomes of brain disorders later in life, this part investigates cardiovascular and socioeconomic risk factors that impact several decades earlier.

Each part of the thesis starts with a list of the included articles, follows briefly with their objectives and a description of methods. Afterwards, the main results are summarized and then discussed in a wider context. The presented studies capitalize on large cohorts of individuals stemming from different populations in a number of countries (Figure 2). We mostly utilized data from four community-based epidemiological studies: CZEch Mental health Study (CZEMS), Survey on Health, Ageing and Retirement in Europe (SHARE), Coronary Artery Risk Development in Young Adults (CARDIA) and Health, Alcohol and Psychosocial factors In Eastern Europe (HAPIEE). In addition, two articles are based on patients registered in the Swedish Dementia Registry (SveDem).

Figure 2 Countries represented in each cohort

CARDIA, Coronary Artery Risk Development in Young Adults; CZEMS, CZEch Mental health Study; HAPIEE, Health, Alcohol and Psychosocial factors In Eastern Europe; SHARE, Survey on Health, Ageing and Retirement in Europe; SveDem, Swedish Dementia Registry

2 Part 1: Epidemiology of brain disorders in the Czech Republic

Study 1: Winkler P, Formanek T, Mlada K, **Cermakova P**. The CZEch Mental health Study (CZEMS): Study rationale, design, and methods. International journal of methods in psychiatric research. 2018;27:e1728[88].

Study 2: Formanek T, Kagstrom A, **Cermakova P**, Csemy L, Mlada K, Winkler P. Prevalence of mental disorders and associated disability: Results from the cross-sectional CZEch Mental health Study (CZEMS). European psychiatry : the journal of the Association of European Psychiatrists. 2019;60:1-6[89].

Study 3: Kagstrom A, Alexova A, Tuskova E, Csajbok Z, Schomerus G, Formanek T, Mlada K, Winkler P, **Cermakova P**. The treatment gap for mental disorders and associated factors in the Czech Republic. European psychiatry : the journal of the Association of European Psychiatrists. 2019;59:37-43[90].

Study 4: Seblova D, Brayne C, Machu V, Kuklova M, Kopecek M, **Cermakova P**. Changes in cognitive impairment in the Czech Republic. Journal of Alzheimer´s Disease. 2019; 72(3):693-701[91].

Study 5: Kucera M, Wolfova K, **Cermakova P**. Changes in depressive symptoms of older adults in the Czech Republic. Journal of Affective Disorders. 2020; 261:139-144[92].

2.1 Objectives

The first part of this thesis examined the burden of mental disorders in the Czech Republic. Specifically, Study 1 describes the methodology of establishing a population-based study of mental disorders in the Czech Republic. Study 2 examined the prevalence of mental disorders and the associated disability in the general population. Study 3 aimed to determine the treatment gap for mental disorders. The objective of Studies 4 and 5 was to find out whether the occurrence of depressive symptoms and cognitive impairment in older adults had changed over time.

2.2 Methods

2.2.1 Participants

Studies 1-3 examined individuals participating in CZEMS, which is a cross-sectional population-based study of mental health in the Czech Republic that has been conducted to support the ongoing mental health care reform. Participants were selected by two-stage sampling, using a random-route-procedure and a first-birthday-method. Data was collected in October/November 2017 by centrally trained staff using a face-to-face paper and pencil interview (PAPI). The response rate was 75% and in total 3 306 individuals (mean age 49 years, 54% women) participated.

Studies 4-5 utilized data from the Czech arm of the SHARE project. SHARE is a longitudinal population-based study that collects information about health, social network and economic conditions of Europeans aged 50 years and older[93]. The participants are followed over time and in addition, refreshment samples of new individuals are enrolled in new waves to compensate for drop out. The first wave of data collection, which is based on computer-assisted personal interview (CAPI), was conducted in 2004 and was followed by six subsequent waves (Figure 3). At baseline, 30 424 individuals (mean age 64 years, 56% women) from 12 countries were recruited and up to the 7th wave, 139 556 individuals from a total of 27 countries completed at least one interview in SHARE project, including the Czech Republic that joined in wave 2.

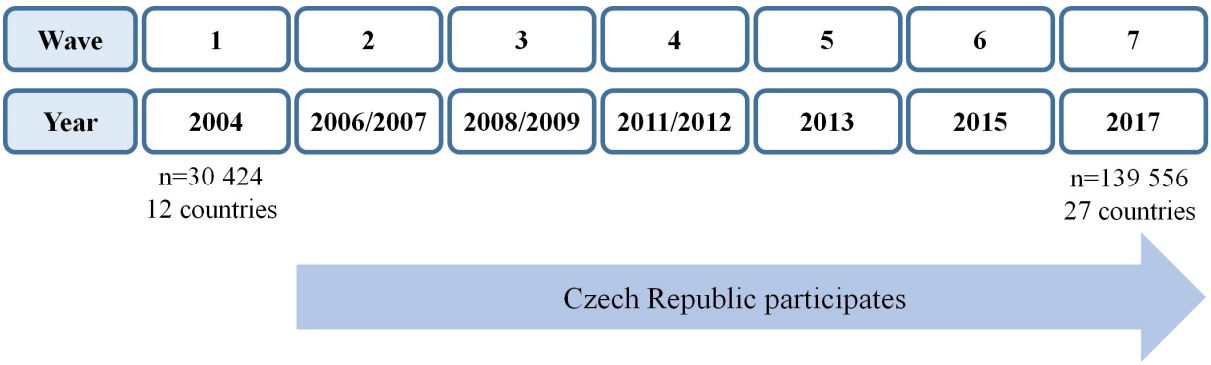

Figure 3 Waves of Survey on Health, Ageing and Retirement in Europe (SHARE) project

2.2.2 Assessment of brain health

The first part of the thesis concerns following brain outcomes: "mental disorders" (Studies 1-3), "cognitive impairment" (Study 4) and "depressive symptoms" (Study 5). In Studies 1-3 based on CZEMS, mental disorders were assessed using Mini International Neuropsychiatric Interview (M.I.N.I.). M.I.N.I. is a fully structured diagnostic interview for the assessment of major psychiatric disorders that allows administration by trained non-specialized interviewers and has been used in numerous previous population-based studies.

The current version of M.I.N.I. consists of 13 modules, each of them referring to a diagnostic category, allowing to diagnose 25 mental disorders. M.I.N.I. enables to diagnose a "current" disorder for all diagnoses, but only some diagnoses have "lifetime" or "past" alternative. We classified individuals with a mental disorder if they fulfilled the criteria for a *current* mental disorder, which we divided into the four following groups (Table 1). Current psychotic disorders were included in Study 2 that dealt with the prevalence of mental disorders, but as previous studies showed strong overestimation of psychosis in lay-administered interviews[94, 95], psychotic disorders were not included in the analysis of the treatment gap in Study 3.

Table 1 Definitions of mental disorders used in Studies 1-3

Group	Included disorders
Affective disorders	major depressive episode, dysthymia, hypomanic episode and manic episode
Anxiety disorders	panic disorder, agoraphobia, obsessive-compulsive disorder, post-traumatic stress disorder, social anxiety disorder and generalized anxiety disorder
Alcohol use disorders	alcohol abuse and alcohol dependence
Substance use disorders	abuse and dependence on stimulants, narcotics, inhalants, cannabis, tranquilizers, psychedelics and other drugs
Psychotic disorders	psychotic disorder

In Study 4, we defined cognitive impairment using four measures (verbal fluency, immediate recall, delayed recall and temporal orientation) acquired from three brief cognitive tests. We coded each cognitive measure into a binary variable indicating impaired vs. normal performance (the cut-off for impaired performance was set at 1.5 standard deviation below the mean)[96]. Participants with impaired performance in at least 2 measures were considered as having cognitive impairment. As participants with missing data on cognition may be more likely to have cognitive impairment, we used 3 scenarios (cognitive impairment 1-3), where we handled missing data in different ways. In addition, we alternatively defined cognitive impairment 4 by constructing a scale from the four cognitive measures and choosing a cut-off (Table 2). To study the change in the prevalence of cognitive impairment, we identified two similar cohorts. "Cohort 1" included participants from the SHARE baseline in wave 2 (2006/2007), while "cohort 2" were those in wave 6 (2015). This allowed us to assess a change in the prevalence of cognitive impairment over an 8-9 years period.

Table 2 Definitions of cognitive impairment

Cognitive impairment	Explanation
Cognitive impairment 1	All individuals with any missing data on cognition were classified as having cognitive impairment.
Cognitive impairment 2	Two proxy variables were used to define cognitive impairment in individuals with incomplete data: 1) self-report of the diagnosis of dementia, senility or Alzheimer´s disease established by a doctor; 2) report (by respondent or proxy) of difficulty in at least one of 3 instrumental activities of daily living[97] - telephone use, taking medication and managing finances.
Cognitive impairment 3	Individuals with any missing data on cognition were excluded.
Cognitive impairment 4	A scale (range 0-16) was constructed from four cognitive measures so that each cognitive measure gave 0-4 points. A cut-off of 6 points was chosen so that individuals reaching the 20% of the lowest distribution of the scale were classified with cognitive impairment[98].

In Study 5, we defined depressive symptoms using the EURO-D scale[99]. It consists of 12 items (depressed mood, pessimism, wishing death, guilt, sleep, interest, irritability, appetite, fatigue, concentration, enjoyment and tearfulness), which are scored either 0 (symptom not present) or 1 (symptom present). The sum of the items generates a scale ranging between 0 and 12, with a higher score suggesting greater severity of depressive symptoms. The cut-off of 4 or more points predicts a high risk of clinical depression. To understand, how the use of medication influenced the change in depressive symptoms, we defined the presence of depressive symptoms in two ways: (1) By reaching 4 or more points on the EURO-D scale or (2) when the individual reported using drugs against depression or anxiety. Similarly to Study 4, we focused on change in the prevalence of depressive symptoms between "cohort 1" in wave 2 of SHARE (2006/2007) and "cohort 2" in wave 6 (2015).

2.2.3 Other variables

Data on all covariates used in Studies 1-3 were gathered as part of the PAPI and are thus self-reported. An important variable used in Study 3 was the "treatment gap" for mental disorders, which has been in previous studies mostly operationalized by utilization of mental health services[100]. We defined it using information on whether the participants sought medical or other professional help

(psychiatrist / psychologist / general practitioner / other professional within the official health care system) due to their mental health during the past 12 months. Another important variable in Study 3 concerned willingness to seek mental health care, which we defined if participants indicated that they were *definitely* willing or *rather* willing to seek a psychiatrist, psychologist or a general practitioner if they experienced mental health problems.

In Studies 1-3, we used data on multiple sociodemographic and health-related covariates either as predictors, confounders or mediators in the analyses. Sociodemographic covariates were age, sex, highest educational attainment, residence, economic activity, marital status, children, informal social contact and a number of stressful life events. Health-related characteristics concerned physical inactivity, diet due to health reasons, smoking and number of somatic diseases. In addition, The World Health Organization Disability Assessment Schedule (WHODAS)[101] measured disability and the Self-Identification as Having a Mental Illness (SELFI) scale was administered to assess self-identification within the group of persons having mental illness[102].

In Studies 4-5, we adjusted the analyses for several sociodemographic and health-related characteristics that were collected as a part of the CAPI and were thus also self-reported. Sociodemographic factors were age, sex, education, household net worth, current job situation, family status, number of children and grandchildren. Health-related characteristics were number of limitations in instrumental activities of daily living (IADL), cardiovascular disease, number of chronic diseases, body mass index (BMI), physical inactivity, smoking, alcohol consumption and maximal grip strength.

2.2.4 Statistical analysis

Selection of the analytical samples is presented on Figure 4. Throughout all of the studies in this thesis, continuous variables with normal distributions were presented as means ± standard deviation (SD), skewed continuous variables as median and interquartile range and categorical variables as frequency (n, %). Differences between two categories were tested using independent samples t-test (continuous normally distributed variables), Mann-Whitney test (continuous skewed variables) or χ^2 test (categorical variables). Differences among more categories were assessed using Analysis of Variance (continuous normally distributed variables), Kruskal-Wallis test (continuous skewed variables) or χ^2 test (categorical variables).

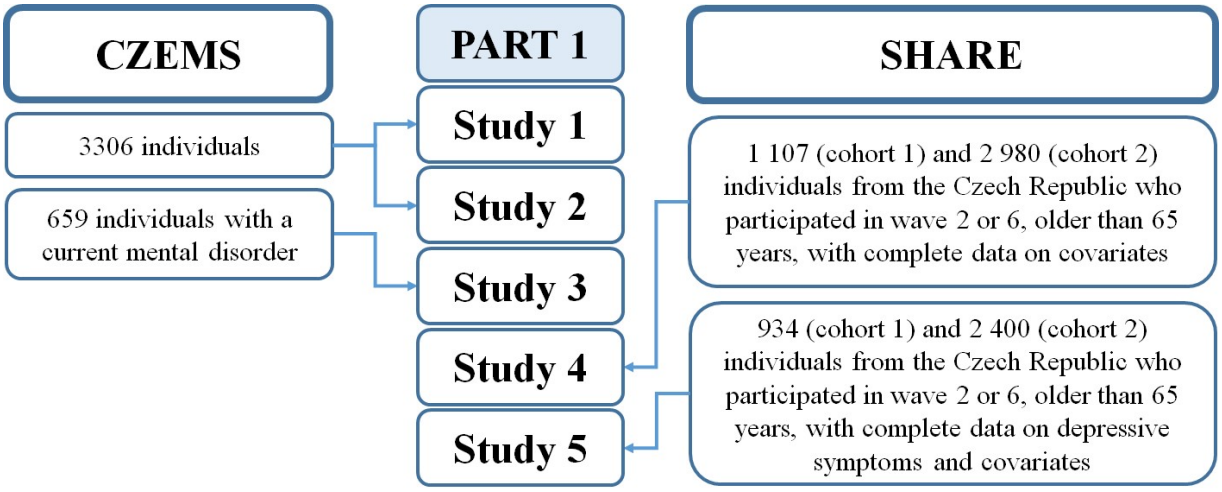

Figure 4 Analytical samples in Part 1

CZEMS, CZEch Mental health Study; SHARE, Survey of Health, Ageing and Retirement in Europe

Study 1 was descriptive and did not contain any multivariable analysis. In Study 2, we employed linear regression to study the association of sociodemographic and health-related characteristics with disability measured by the WHODAS scale, which had been log-transformed due to skewed distribution (this analysis is not presented in this thesis). In Study 3, we applied binary logistic regression to estimate odds ratios (OR) with 95% confidence intervals (CI) for the associations of respondent´s sociodemographic and health-related factors with the utilization of mental health services. We also used structural equation modelling (SEM) to estimate with logistic regression the OR with 95% CI for the association of respondents´ characteristics with willingness to seek mental health care. The SEM analysis enabled the estimation of all hypothesized paths' coefficients between all the characteristics of the participants and the willingness to seek each of the three professionals (a general practitioner, a psychologist and a psychiatrist) simultaneously.

In Studies 4 and 5, we analysed whether the prevalence of cognitive impairment / depressive symptoms changed over time in the following way: we used binary logistic regression to estimate OR with 95% CI for the association of cohort 2 (relative to cohort 1) with cognitive impairment / depressive symptoms, step-wise adjusting for groups of sociodemographic and health-related covariates. An OR lower than 1 would indicate lower prevalence of cognitive impairment / depressive symptoms in cohort 2. In order to examine the extent the covariates explained the differences in the prevalence of cognitive impairment / depressive symptoms between cohort 1 and 2, we used multivariate decomposition for nonlinear models[103].

2.3 Results

2.3.1 Prevalence of mental disorders and associated treatment gap (Studies 1-3)

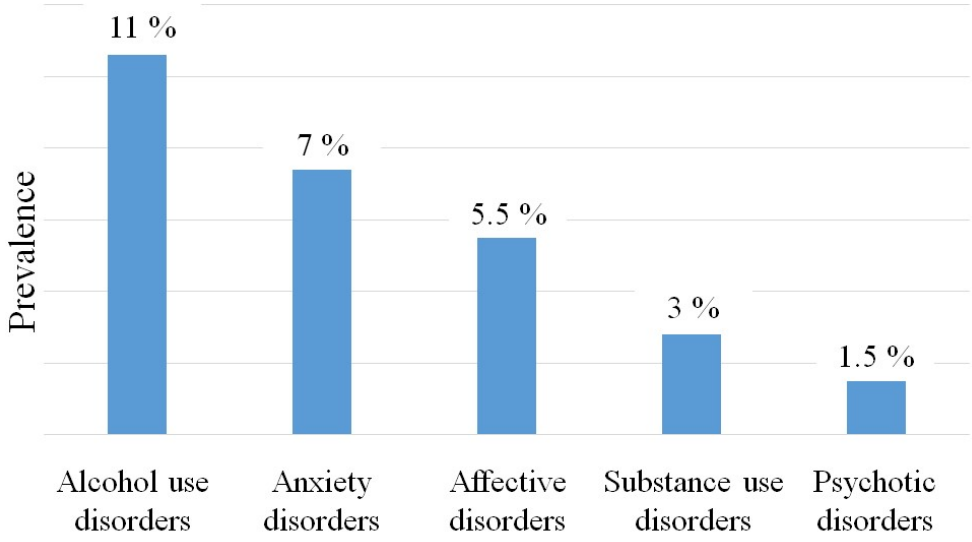

Figure 5 Prevalence of mental disorders; data from CZEch Mental health Study (CZEMS)

Among the 3 306 participants of CZEMS (mean age 49 years, 54% women), 22% had at least one current mental disorder. The most common group were alcohol use disorders (11%), followed by anxiety disorders (7%), affective disorders (5.5%), substance use disorders (3%) and psychotic disorders (1.5%; Figure 5).

Treatment gap, operationalized by no reported utilization of mental health services, ranged from 61% for affective disorders to 93% for alcohol use disorders (Figure 6). Utilization of mental health services was associated with being a woman (OR 3.31; 95% CI 1.97 to 5.57), residence in bigger communes (OR 1.84; 95% CI 1.12 to 3.04), higher number of somatic diseases (OR 1.32; 95% CI 1.03 to 1.67) and a higher score in disability (OR 1.04; 95% CI 1.02 to 1.05; Table 3).

In individuals classified with a mental disorder who did not utilize mental health services, willingness to seek a psychiatrist was associated with being a woman, residence in smaller communes, higher disability and higher self-identification with people with a mental illness measured on SELFI scale. Willingness to seek a psychologist was also related to female sex and higher score on SELFI, but also to younger age, higher education and lack of smoking. On the other hand, higher age and a higher number of somatic diseases were associated with willingness to seek a general practitioner.

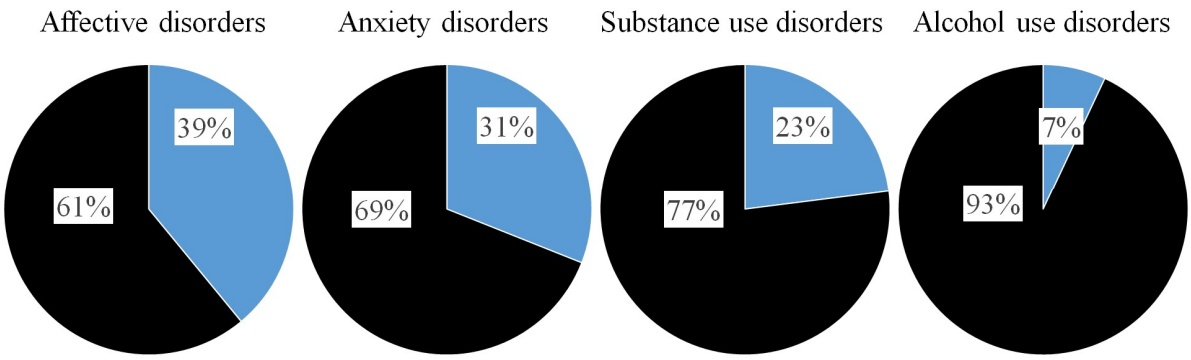

Figure 6 Treatment gap for mental disorders; data from CZEch Mental health Study (CZEMS)

Note: Blue indicates share of people that utilize mental health services; black indicates the treatment gap

Table 3 Associations of participants' characteristics with utilization of mental health services, data from CZEch Mental health Study (CZEMS)

	OR (95% CI)
Age	0.99 (0.97; 1.00)
Women	3.31 (1.97; 5.57)**
Residence in a commune with more than 5000 inhabitants	1.84 (1.12; 3.04)*
Without work	1.75 (0.95; 3.21)
Without partner	1.43 (0.87; 2.34)
Little informal social contact	1.03 (0.60; 1.76)
Stressful life events (≥4)	0.97 (0.59; 1.58)
Physical inaktivity	1.58 (0.91; 2.73)
Diet due to health reasons	0.99 (0.56; 1.75)
Number of somatic diseases	1.32 (1.03; 1.67)*
WHODAS score (disability)	1.04 (1.02; 1.05)**

OR, odds ratio; CI, confidence interval; WHODAS, The World Health Organization Disability Assessment Schedule; *p<0.05; **p<0.001

2.3.2 **Trends in cognitive impairment and depressive symptoms** (Studies 4-5)

In the sample for the study of the longitudinal change in cognitive impairment (n=1071 in cohort 1 and n=3104 in cohort 2), respondents in cohort 2 scored higher in all brief cognitive tests and had thus a lower prevalence of cognitive impairment. When classifying all individuals with missing data as cognitively impaired (cognitive impairment 1), the prevalence of cognitive impairment was 11%

in cohort 1 and 9% in cohort 2 (absolute decrease=1.2 times). When we used proxy-variables to indicate cognitive impairment 2, its share was 11% in cohort 1 and 7% in cohort 2 (absolute decrease=1.6 times). Analysing only complete cases (cognitive impairment 3), the prevalence was 9% in cohort 1 and 4% in cohort 2 (absolute decrease=2.3 times). When a summary scale was used (cognitive impairment 4), the prevalence was 31% in cohort 1 and 17% in cohort 2 (absolute decrease=1.8 times).

Cohort 2 was significantly associated with lower odds of cognitive impairment 1, adjusting for age, sex and birth cohort. The association was attenuated and lost statistical significance when education was added into the model. The trends were similar for cognitive impairment 2, 3 and 4, but the associations remained statistically significant even after the step-wise adjustments (Table 4). The changes in prevalence of cognitive impairment were attributable to an increase in physical activity, receiving medication for high blood cholesterol, longer education and reduction in stroke. On the contrary, the increased share of individuals with high blood cholesterol had negatively influenced the observed prevalence changes.

Table 4 Association of cohort 2 (2015) related to cohort 1 (2006/2007) with cognitive impairment; data from Survey on Health, Ageing and Retirement in Europe (SHARE)

	Cognitive impairment 1	Cognitive impairment 2	Cognitive impairment 3	Cognitive impairment 4
Model 1	0.59 (0.37; 0.95)*	0.40 (0.24; 0.66)**	0.31 (0.18; 0.53)**	0.28 (0.19; 0.42)**
Model 2	0.67 (0.41; 1.08)	0.45 (0.27; 0.75)*	0.36 (0.20; 0.62)**	0.33 (0.22; 0.50)**
Model 3	0.72 (0.43; 1.21)	0.46 (0.27; 0.80)*	0.38 (0.21; 0.68)*	0.34 (0.22; 0.53)**

Results are odds ratios with 95% confidence intervals derived from binary logistic regression
*p<0.05; **p<0.001

Model 1: age, sex, birth cohort
Model 2: age, sex, birth cohort, education
Model 3: age, sex, birth cohort, education, living with a spouse, net worth, currently working, stroke, myocardial infarction, high blood pressure or hypertension, high blood cholesterol, high blood sugar or diabetes mellitus, drugs for high blood pressure, drugs for cholesterol, drugs for diabetes mellitus, drugs for coronary heart disease, depression, alcohol, obesity, physical inactivity

The analytical sample for the study of the change in depressive symptoms consisted of 1107 participants in cohort 1 and 2972 in cohort 2 (mean age 72 years, 58% women in both cohorts). When defining depressive symptoms using the EURO-D scale, their prevalence was 28% in cohort

1 and 22% in cohort 2 ($p<0.001$ from χ^2 test). In multivariable analysis, cohort 2 was associated with a lower likelihood of depressive symptoms in the age-sex adjusted model (OR 0.75; 95% CI 0.64 to 0.88; Table 5, Model 1). This association weakened but remained statistically significant after further controlling for all sociodemographic and health-related factors (OR 0.77; 95% CI 0.63 to 0.94; Model 4; Table 5).

When depressive symptoms were operationalized by the EURO-D scale and/or use of drugs, their prevalence was 30% in cohort 1 and 26% in cohort 2 ($p<0.001$). Using regression modelling, the association of cohort 2 with a lower likelihood of depressive symptoms was weaker in magnitude (OR 0.84; 95% CI 0.72 to 0.99; Model 1; Table 5) compared to the definition with EURO-D scale only. When controlling for education, the association was reduced even more and became statistically non-significant (OR 0.89; 95% CI 0.76 to 1.05; Model 3). The OR in the fully adjusted model was 0.88 (95% CI 0.73 to 1.07; Model 4). The multivariate decomposition indicated the decrease in depressive symptoms was attributable to more years of education and higher household net worth, but was negatively influenced by higher number of chronic diseases and limitations in IADL in cohort 2.

Table 5 Association of cohort 2 (2015) related to cohort 1 (2006/2007) with depressive symptoms; data from Survey on Health, Ageing and Retirement in Europe (SHARE)

	Depressive symptoms defined by EURO-D scale	Depressive symptoms defined by EURO-D scale or use of drugs
Model 1	0.75 (0.64; 0.88)**	0.84 (0.72; 0.99)*
Model 2	0.79 (0.67; 0.93)*	0.89 (0.76; 1.05)
Model 3	0.79 (0.66; 0.94)*	0.88 (0.75; 1.04)
Model 4	0.77 (0.63; 0.94)*	0.88 (0.73; 1.07)

Results are odds ratio with 95% confidence intervals derived from binary logistic regression
*p<0.05; **p<0.001

Model 1: age, sex
Model 2: age, sex, years of education
Model 3: age, sex, years of education, rural residence, household net worth, civil status, children, grandchildren
Model 4: age, sex, years of education, rural residence, household net worth, civil status, children, grandchildren, cardiovascular disease, cognitive impairment, number of chronic diseases, physical inactivity, obesity, limitations in instrumental activities of daily living, maximal grip strength

2.4 Discussion

In a nationally representative sample of community-dwelling adults in the Czech Republic, we found that 22% of individuals were affected by at least one current mental disorder. The most common group of mental disorders were alcohol use disorders. The majority of people who were classified with a mental disorder did not use professional mental health care. This gap was highest for alcohol use disorders and smallest for affective disorders. Among Czech community-dwelling adults older than 65 years, we observed an optimistic trend suggesting that the age-specific prevalence of cognitive impairment and depressive symptoms decreased over the last decade.

These findings need to be discussed in the context of the methodology of the performed studies. The results of the CZEMS study on the prevalence of mental disorders and the associated treatment gap are generalizable only to community-dwelling individuals. Individuals who were not included in this study were those who did not want to participate in a research study and homeless people. It can be speculated that they are more likely to have worse mental health than the participants, which may underestimate the prevalence of mental disorders. Individuals institutionalized due to a mental disorder were not included in CZEMS either, which underestimates the prevalence and at the same time overestimates the extent of the treatment gap we found. In addition, the way the treatment gap was operationalized does not take into account effective or evidence-based treatment. In addition, the classification of mental disorders in this study was made based on the presence of current symptoms. Thus, people diagnosed with mental disorders who were successfully treated at the time of the interview and did not present with symptoms were not included in the analysis, which further underestimates the prevalence and overestimates the treatment gap.

Despite the aforementioned limitations, results of the CZEMS study offer a good insight into the situation of community-dwelling individuals who are experiencing symptoms of mental disorders. The prevalence of alcohol use disorders including alcohol abuse and dependence is extremely high. Specifically, the prevalence of alcohol dependence in the Czech Republic is almost twice as high as overall European estimates[3]. One of the largest studies on alcohol concluded that there are no real health benefits of even mild to moderate alcohol consumption on health[104], emphasizing the need for policies aiming to prevent alcohol use disorders. Similarly to the global literature on treatment gap[100], our results show that the majority of people classified with mental disorders do not receive any health care. This large treatment gap could be narrowed through several strategies that aim to either increase

the accessibility of mental health services (increase in number of both psychiatric and non-psychiatric human resources) or their utilization (reduction of stigma and increase in mental health literacy). Special emphasis needs to be placed on the decentralization of mental health services as rural areas are now underserved. Mental health promotion targeting men can be achieved with an appropriate language, focusing on mental strength and well-being in the workplace.

The study sample based on SHARE is not entirely representative of the population of older adults. As participants in surveys are usually healthier and more educated than the general population, this possibly underestimates the burden of depression and cognitive impairment we found in our studies. The exclusion of institutionalized individuals from the sampling frame likely also underestimates the prevalence of depressive symptoms and cognitive impairment at both time points. If the prevalence of institutionalized individuals in the country increased from 2006/2007 to 2015, the observed decline in depressive symptoms may be overestimated.

The decline in the age-specific prevalence of cognitive impairment is well in line with a large number of studies that have been predominantly conducted in high income countries and suggest stable or declining incidence and age-specific prevalence of dementia / cognitive impairment[58, 59]. In our study, the majority of the lower cognitive impairment prevalence in 2015 was explained by reductions in physical inactivity, improved control of high blood cholesterol, increases in the length of education and decline in stroke occurrence. However, increased proportion of individuals with high blood cholesterol may be slowing down the improvements in cognitive health in the Czech Republic. A further increase in population education and decrease in cardiovascular risk factors may yield an even larger decrease.

On the contrary, the decline in depressive symptoms is not a consistent finding in the literature, as several authors report no change or even an increase in the prevalence of depression[105, 106]. However, our results are in accord with findings from the USA, where Zivin et al found a reduction over time in the elevated depressive symptoms in individuals in later adulthood[107]. We found that the difference in depressive symptoms between the cohorts was not fully explained by improved treatment of depression, as increased length of education and better socioeconomic resources in the household also contributed to the decline. This is in line with a large body of previous evidence on socioeconomic inequalities in depression[78]. High education and socioeconomic resources can promote the feeling of control over life, independence, sense of mastery and self-efficacy as well as

cognitive and socioemotional skills that enable coping with life's problems and stresses. The increase in the socioeconomic level over time has likely outweighed the impact of disability and multimorbidity on depressive symptoms. We suggest that an even larger decrease in depressive symptoms could be possible in the Czech Republic by enabling the population to reach higher education and gain more socioeconomic resources. We further speculate that targeting disability could help to further reduce depressive symptoms of older adults.

3 Part 2: Depressive symptoms and cognitive health in older Europeans

Study 6: Horackova K, Kopecek M, Machu V, Kagstrom A, Aarsland D, Motlova LB, **Cermakova P**. Prevalence of late-life depression and gap in mental health service use across European regions. European psychiatry : The Journal of the Association of European Psychiatrists. 2019;57:19-25[108].

Study 7: Formanek T, Kagstrom A, Winkler P, **Cermakova P.** Differences in cognitive performance and cognitive decline across european regions: A population-based prospective cohort study. European psychiatry : the journal of the Association of European Psychiatrists. 2019;58:80-86[109].

Study 8: Cermakova P, Nelson M, Secnik J, Garcia-Ptacek S, Johnell K, Fastbom J, Kilander L, Winblad B, Eriksdotter M, Religa D. Living alone with Alzheimer's disease: Data from SveDem, the Swedish Dementia Registry. Journal of Alzheimer's disease : JAD. 2017;58:1265-1272[21].

Study 9: Secnik J, **Cermakova P**, Fereshtehnejad SM, Dannberg P, Johnell K, Fastbom J, Winblad B, Eriksdotter M, Religa D. Diabetes in a large dementia cohort: Clinical characteristics and treatment from the Swedish Dementia Registry. Diabetes Care. 2017;40:1159-1166[23].

3.1 Objectives

In the second part of the thesis, we focused on several issues surrounding mental health of older adults in different European countries. Studies 6 and 7 aimed to determine how four European regions differ in the prevalence of depressive symptoms, the level of cognitive performance and the rate of cognitive decline. The objectives of Studies 8 and 9 were to establish whether living alone and being affected by DM influenced the management of dementia in Sweden.

3.2 Methods

3.2.1 Participants

Studies 6 and 7 were based on SHARE participants (see previous chapter for description). Patients registered in the Swedish Dementia Registry (SveDem) are the basis for Studies 8 and 9. SveDem is a web-based registry of patients with dementia in Sweden. It was established in May 2007 with the aim to register all patients at the time of the dementia diagnosis in Sweden, follow them up and

monitor their care[110]. Data about their age, sex, family history of dementia, BMI, global cognitive status using Mini Mental State Examination (MMSE) score, content of diagnostic work-up, type of dementia disorder, pharmacological and non-pharmacological treatment and support for the patient from the county and municipality as well as standard demographic information were registered. Patients were registered either by a specialist (geriatrician) in a memory clinic or a general practitioner in a primary care unit. This thesis used SveDem data up to 2015, when 58 154 patients were registered (mean age at the time of diagnosis was 80 years, 59% women).

3.2.2 Assessment of brain health

The second part of the thesis concerns the following brain outcomes: "depressive symptoms" (Study 6), "cognition" (Study 7) and "dementia" (Studies 8-9). Studies 6 and 7 based on SHARE utilized measurements of depressive symptoms and cognition described in the previous chapter. Depressive symptoms were defined by reaching 4 or more points on EURO-D scale and cognitive performance was assessed with measures of verbal fluency, immediate recall and delayed recall. An overall cognitive score was created from the three cognitive measures.

Clinical diagnosis of dementia was available in Studies 8 and 9 that were based on SveDem. The diagnosis was established either by geriatricians or general practitioners (who in Sweden are uniquely "allowed" to diagnose dementia) and was recorded as AD, vascular dementia, mixed dementia (AD/vascular dementia), dementia with Lewy bodies, Parkinson´s disease dementia, frontotemporal dementia, unspecified dementia or other. Physicians were instructed to diagnose patients based on the 10th revision of the International Classification of Diseases (ICD 10) criteria and the following specific criteria: McKeith criteria for dementia with Lewy bodies[111], Lund-Manchester criteria for frontotemporal dementia[112] and the Movement Disorder Society Task Force criteria for Parkinson´s disease dementia[113]. Unspecified dementia was recorded if the dementia etiology was unknown or if investigations aimed to differentiate the type of dementia have not been performed. Other dementia types comprised of rare dementia disorders that were represented, for example, by corticobasal degeneration or alcoholic dementia.

3.2.3 Other variables

In Study 6 based on SHARE, we operationalized the utilization of mental health services by combining two pieces of information: self-reported diagnosis (when the participants positively

answered a question whether they have been told by a doctor that they have affective or emotional disorders) and self-reported medication (when the participants answered positively to a question whether they are using drugs against depression or anxiety). Other variables from SHARE used in Studies 6 and 7 have been described in previous chapters.

Data on living condition in Study 8 based on SveDem was acquired at the time of dementia diagnosis and was recorded into the registry as "living alone / living with another adult / don't know". In Study 9 based on SveDem data, information on DM was acquired from the Swedish Patient Register and the Swedish Prescribed Drug Register, which were merged to the data from SveDem, using a unique personal number. Specifically, DM was defined by the ICD-10 code E10–E13 when present at any position (main diagnosis or additional diagnoses) or by the administration of antidiabetic drugs, coded with A10, using the Anatomical Therapeutical and Chemical (ATC) Classification system.

In Studies 8 and 9, we also used data on utilization of procedures for the diagnostic dementia work-up and prescription of psychotropic medications. Performance of basic or extended diagnostic work-up was registered in SveDem at the time of dementia diagnosis. Basic dementia-work up included MMSE, clock test, blood chemistry test, and computerized tomography (CT). Extended diagnostic tests included, among others, lumbar puncture (LP), use of magnetic resonance imaging (MRI) and neuropsychological testing. Data on drugs were extracted from the Swedish Prescribed Drug Register, coded according to the ATC Classification system as: cholinesterase inhibitors (N06DA), memantine (N06DX01), antidepressants (N06A), anxiolytics (N05B), antipsychotics (N05A), hypnotics and sedatives (N05C).

3.2.4 Statistical analysis

Derivation of analytical samples is presented on Figure 7. In Study 6, we utilized binary logistic regression to assess the association of participants´ characteristics with depressive symptoms. Among individuals with depressive symptoms, binary logistic regression assessed the association of participants´ characteristics with the utilization of mental health services. We performed dominance analysis to calculate the relative importance of each covariate in the final models and the proportion of variance explained by them[114].

In Study 7, we employed linear regression to estimate B coefficients with 95% CI for the associations of European regions (used as dummy variables, with Western Europe as reference category) with

the level of cognitive performance. In addition, we conducted longitudinal analysis to study how the European regions differ in the rate of cognitive decline, by constructing linear mixed models with the respondents set as random intercepts, the time in years between waves of study as a random slope and also as fixed effect and all covariates as fixed effects.

In Study 8, we assessed with binary logistic regression the association of several diagnostic tests and medications with solitary living, adjusting for age, sex, setting of registration (primary care vs. specialist unit), dementia type, MMSE score at the time of registration and comorbidities (total number of drugs[115] or Charlson Comorbidity Index[116]).

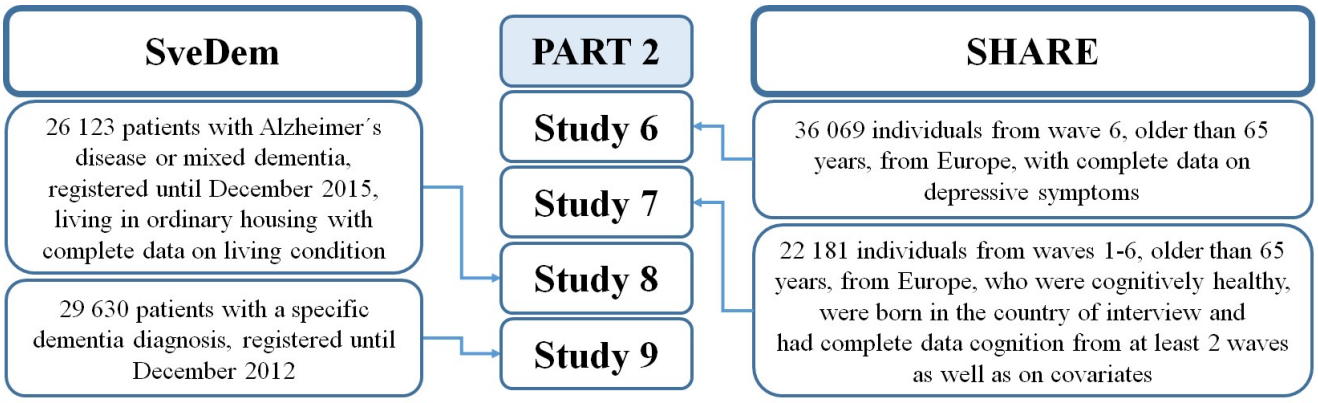

Figure 7 Analytical samples in Part 2

SHARE, Survey on Health, Ageing and Retirement in Europe; SveDem, Swedish Dementia Registry

3.3 Results

3.3.1 Depressive symptoms and cognition in European regions (Studies 6-7)

In 36 069 older adults from Europe (55% women; mean age 74 years old), 10 483 (29%) had depressive symptoms (reaching at least 4 points on the EURO-D scale). The prevalence was highest in Southern Europe (35%), followed by CEE (32%), Western Europe (26%) and the lowest in Scandinavia (17%; Figure 4). The most important factors associated with depressive symptoms were total number of chronic diseases, pain, limitations in IADL, grip strength and cognitive impairment. The importance of these factors did not largely differ by European regions.

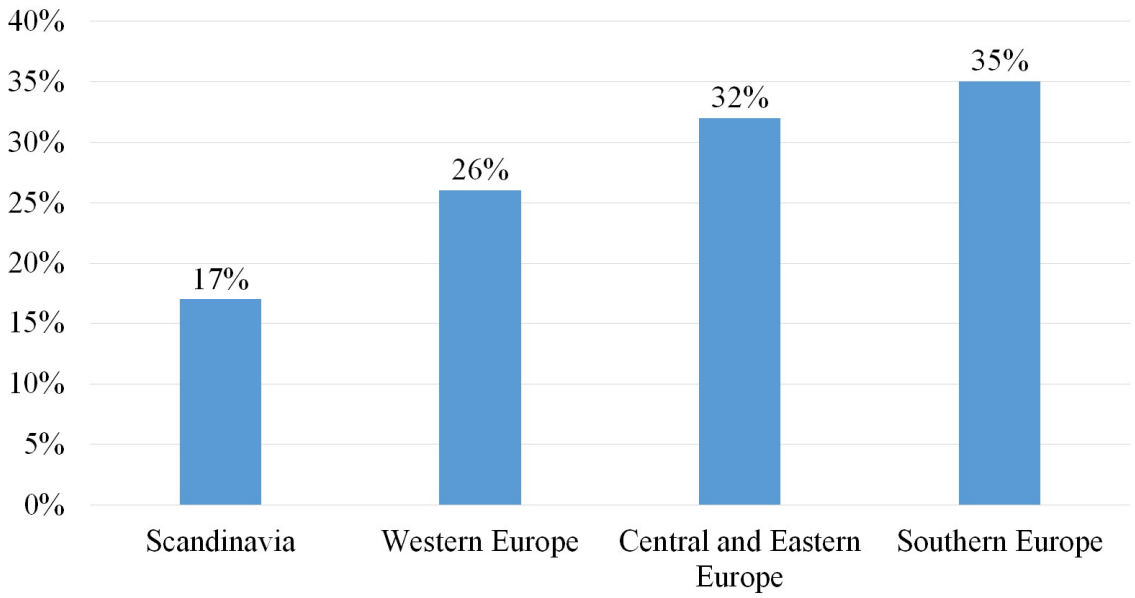

Figure 8 Prevalence of depressive symptoms in European regions; data from Survey of Health, Ageing and Retirement in Europe (SHARE)

Among people with depressive symptoms, the gap in utilization of mental health services was 79% in the whole sample and was lower in Western and Southern Europe (both 76%) and higher in Scandinavia and CEE (both 83%). The utilization of mental health services was associated with a lower age, female sex, cognitive impairment, higher number of chronic diseases, lower BMI and a higher number of limitations in IADL (Table 4). The most dominant factor was largely the number of chronic diseases.

Table 6 Associations of individual characteristics with utilization of mental health services in persons with depressive symptoms (n=7 645); data from Survey of Health, Ageing and Retirement in Europe (SHARE)

	OR (95% CI)
Age	0.96 (0.95; 0.97)**
Women	1.51 (1.26; 1.80)**
Years of education	0.99 (0.98; 1.00)
Cognitive impairment	1.20 (1.05; 1.38)*
Number of chronic diseases	1.44 (1.39; 1.49)**
Troubled by pain	0.96 (0.83; 1.10)
Physical inactivity	0.94 (0.81; 1.10)
BMI	0.98 (0.97; 0.99)*
Limitations in IADL	1.12 (1.08; 1.16)**
Maximal grip strength	0.99 (0.99; 1.00)
Alcohol	0.98 (0.87; 1.11)

OR, odds ratio; CI, confidence interval; BMI, body mass index; IADL, instrumental activities of daily living; *p<0.05; **p<0.001

In the sample for the study of differences in cognition among Europeans (22 181 individuals; 54% women; median age 71 years), participants from Scandinavia reached the highest scores in all cognitive tests, followed by Western Europe, CEE and Southern Europe. These differences were not explained by age, sex or sociodemographic or health-related characteristics. When compared to Western Europe and adjusting for a wide range of sociodemographic and health-related factors, Scandinavia was associated with higher level of overall cognitive performance (B 0.07; 95% CI 0.05 to 0.10), while CEE (B -0.14; 95% CI -0.16 to -0.11) as well as Southern Europe with a lower level (B -0.44; 95% CI -0.46 to -0.41; Table 7A).

Surprisingly, the annual decline in the composite cognitive score was considerably higher in Scandinavia (0.59%), than in Western Europe (0.28%), CEE (0.25%) and Southern Europe (0.23%), when adjusted for baseline age and sex. Adding sociodemographic and health-related factors into the models attenuated the differences. Then, the highest rate of annual decline in composite cognitive score was still in Scandinavia (0.49%), while the 3 other regions had a similarly lower rate of cognitive decline: Western Europe 0.18%, Southern Europe 0.17% and CEE 0.16% (Table 7B).

Table 7 Cognitive performance and rate of cognitive decline in European regions, data from Survey of Health, Ageing and Retirement in Europe (SHARE)

A) Level of cognitive performance		
	Model 1	Model 2
Western Europe	Reference	
Scandinavia	0.14 (0.11; 0.17)**	0.07 (0.05; 0.10)**
CEE	-0.13 (-0.16; -0.11)**	-0.14 (-0.16; -0.11)**
Southern Europe	-0.61 (-0.63; -0.58)**	-0.44 (-0.46; -0.41)**
B) Rate of cognitive decline		
Western Europe	-0.28 (-0.33; -0.23)**	-0.18 (-0.23; -0.13)**
Scandinavia	-0.59 (-0.66; -0.53)**	-0.49 (-0.56; -0.43)**
CEE	-0.25 (-0.33; -0.17)**	-0.16 (-0.24; -0.08)**
Southern Europe	-0.23 (-0.28; -0.19)**	-0.17 (-0.21; -0.13)**

A) Results are unstandardized B coefficients with 95% confidence intervals as well as standardized beta coefficients, derived from linear regression that was used to determine the association of European regions (dummy coded) with the baseline overall cognition (average of z-scores of verbal fluency, immediate recall and delayed recall), in comparison with Western Europe.

B) Results are unstandardized B coefficients with 95% confidence intervals, derived from linear mixed models, representing the annual decline in % of the composite cognitive score.

**p<0.001; CEE, Central and Eastern Europe; Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, education, civil status, employment status, residence, cardiovascular disease, physical inactivity, body mass index, smoking, alcohol and depressive symptoms

3.3.2 Gaps in management of Swedish patients with dementia

From 26 123 patients registered to SveDem with the diagnosis of AD or mixed dementia (62% women; mean age 80 years), 11 878 (46%) lived alone at the time of the diagnosis. Solitary living was associated with lower odds of receiving several diagnostic tools, such as CT (OR 0.89; 95% CI 0.82 to 0.97), MRI (OR 0.90; 95% CI 0.83 to 0.98) and LP (OR 0.86; 95% CI 0.81 to 0.91), even when adjusted for age, sex, MMSE, diagnosis of mixed dementia and comorbidities (Table 8). Patients who lived alone had also lower odds of receiving cholinesterase inhibitors (OR 0.80; 95% CI 0.76 to 0.85) and memantine (OR 0.75; 95% CI 0.70 to 0.80), but higher odds of being prescribed antidepressants (OR 1.11; 95% CI 1.05 to 1.18), antipsychotics (OR 1.39; 95% CI 1.24 to 1.56) and sedatives (OR 1.08; 95% CI 1.01 to 1.15).

Table 8 Associations of diagnostic examinations and psychotropic medications with solitary living, data from the Swedish Dementia Registry (SveDem)

	OR (95% CI)
Diagnostic examinations	
MMSE	1.00 (1.00; 1.01)
Clock test	0.91 (0.82; 1.01)
Blood chemistry	0.93 (0.79; 1.09)
CT	0.89 (0.82; 0.97)*
MRI	0.90 (0.83; 0.98)*
LP	0.86 (0.81; 0.97)**
Neuropsychological examination	0.97 (0.91; 1.04)
Psychotropic medication	
Cholinesterase inhibitors	0.80 (0.76; 0.85)**
Memantine	0.75 (0.70; 0.80)**
Antidepressant drugs	1.11 (1.05; 1.18)**
Anxiolytic drugs	0.96 (0.89; 1.02)
Antipsychotic drugs	1.39 (1.24; 1.56)**
Hypnotics/sedatives	1.08 (1.01; 1.15)*

MMSE, Mini Mental State Examination; CT, computerized tomography; MRI, magnetic resonance imaging; LP, lumbar puncture; OR, odds ratio; CI, confidence interval; *p<0.05; **p<0.001.

Each predictor in the table was entered into the model separately. Each model was adjusted for age, sex, MMSE, diagnosis of mixed dementia and Charlson Comorbidity Index. Model adjusted for total number of drugs as another measure of comorbidity yielded almost identical results.

From 29 630 patients with dementia, 16.5% were identified as having DM. Among patients with dementia, DM was associated with younger age at the time of registration into SveDem (OR 0.97; 95% CI 0.97 to 0.98), being a man (OR 1.41; 95% CI 1.27 to 1.55), lower MMSE score (OR 0.98; 95% CI 0.97 to 0.99) and a higher total number of drugs (OR 1.15; 95% CI 1.13 to 1.17). Relative to AD, patients with DM were more likely to have the diagnosis of mixed dementia (OR 1.21; 95% CI 1.06 to 1.36) and vascular dementia (OR 1.17; 95% CI 1.01 to 1.36), but they had lower odds of being diagnosed with dementia with Lewy bodies (OR 0.64; 95% CI 0.44 to 0.94) and Parkinson´s disease dementia (OR 0.46; 95% CI 0.28; 0.75). Patients with DM had also lower odds of being prescribed cholinesterase inhibitors (OR 0.77; 95% CI 0.69 to 0.85), mematine (OR 0.78; 95% CI 0.68 to 0.89), hypnotics/sedatives (OR 0.82; 95% CI 0.73 to 0.91) and antidepressants (OR 0.85; 95% CI 0.77 to 0.94; Table 9).

Table 9 Associations of dementia patients´ characteristics with diabetes mellitus, data from the Swedish Dementia Registry (SveDem)

	OR (95% CI)
Age	0.97 (0.97; 0.98)**
Male sex	1.41 (1.27; 1.55)**
Institutional living	0.93 (0.74; 1.18)
Living alone	1.10 (0.99; 1.22)
Registered by specialist	0.94 (0.84; 1.05)
MMSE	0.98 (0.97; 0.99)**
Total number of drugs	1.15 (1.13; 1.17)**
Dementia type	
Alzheimer´s disease	Reference
Mixed dementia	1.21 (1.06; 1.39)**
Vascular dementia	1.17 (1.01; 1.36)**
Dementia with Lewy bodies	0.64 (0.44; 0.94)**
Frontotemporal dementia	1.12 (0.76; 1.65)
Parkinson´s disease dementia	0.46 (0.28; 0.75)**
Unspecified dementia	1.08 (1.05; 1.33)
Psychotropic medication	
Cholinesterase inhibitors	0.77 (0.69; 0.85)**
Memantine	0.78 (0.68; 0.89)**
Antipsychotics	1.08 (0.93; 1.24)
Anxiolytics	1.03 (0.91; 1.15)
Hypnotics/sedatives	0.82 (0.73; 0.91)**
Antidepressants	0.85 (0.77; 0.94)**

All factors in this table were entered into the model. In addition, the model is also adjusted for antithrombotic, cardiac, antihypertensive drugs and statins.

OR, odds ratio; CI, confidence interval; MMSE, Mini Mental State Examination; **p<0.001

3.4 Discussion

The presented studies demonstrated a large variation in brain health of older adults residing in different European regions. Individuals from Southern Europe as well as CEE showed a markedly higher level of depressive symptoms and a lower level of cognitive performance when compared to their counterparts in Western Europe and Scandinavia. Surprisingly, even though Scandinavians had the highest levels of cognitive performance, they also showed the highest rate of annual cognitive decline over time. Furthermore, we observed several gaps in the management of patients with dementia in Sweden. In particular, patients with dementia who lived alone at the time of their diagnosis as well as patients who had DM as a comorbidity were less likely to be treated with anti-dementia medications.

The regional differences in depressive symptoms are in line with the majority[50-52], but not all[117], Europe-wide comparisons as well as with the global literature suggesting a higher burden of depression in countries with poorer living conditions[118, 119]. Possibly, richer and stronger welfare states may reduce the burden of depressive symptoms in older adults by supporting them to be independent and providing social and public services. The gap in the use of mental health services in older adults with depressive symptoms is high across all European regions. The strong association between the higher number of somatic disorders with utilization of mental health services indicates that depressive symptoms may emerge unnoticed in adults who do not often visit physicians due to somatic diseases. This large gap could be addressed by promoting help-seeking behaviour in older adults, reducing stigma and ageism in society, which are strong barriers to the utilization of mental health services[120-123].

Our findings on the regional variation in the level of cognitive performance complement previous studies on geographical inequalities in human cognitive capital in different age groups[55, 56, 124-129]. In line with literature[55, 56], we show that Scandinavians have the highest level of cognitive performance in Europe, adding a counterintuitive finding that they have the fastest rate of cognitive decline. These seemingly discrepant results could be explained using the construct of cognitive reserve, which may be mirrored in the baseline level of cognitive performance. Several authors suggest that individuals with the greatest cognitive reserve, as indicated by the most favourable socioeconomic position, experienced a faster rate of cognitive decline when compared to individuals with a less advantageous position[130, 131]. With a large cognitive reserve, which could be a consequence of advantages

associated with strong welfare states that enable the citizens to engage in intellectually stimulating occupations and other reserve enhancing activities over the whole life-course[132, 133], there are more neural resources to lose. Thus, having a higher cognitive reserve during the life-course may be followed by a greater rate of cognitive decline, once the mechanisms that protect the brain against accumulating pathology have been depleted.

There is no disease-modifying treatment against dementia available today. The only medications that can be offered to patients of AD, the most common type of dementia, are cholinesterase inhibitors and memantine[87]. Our studies identified some barriers in the prescription of these drugs, one of which is solitary living, which was found high in the sample of Swedish AD patients at the time of their diagnosis (46%). Of note is that the share of solitary living AD patients was likely underestimated as we excluded patients with unspecified dementia from the sample. They may have AD, but were not diagnosed with it, likely due to their high age, comorbidities or even solitary living. In addition, it is possible that patients who live alone are less likely to be registered to SveDem, which further underestimates the number of solitary living AD patients.

Patients who lived alone were also examined less intensively with the use of CT as well as more advanced tests, such as MRI and LP. These results indicate that a partner or a close caregiver may influence diagnostic as well as therapeutic decisions, likely because they may insist on therapy and adequate tests, can secure adherence to drugs and manage their side effects. We suggest that solitary living persons should receive more support when undergoing investigations for the diagnosis of dementia as well as more support in the management of their medications. In addition, patients who lived alone were more likely to be prescribed antidepressants, antipsychotics and hypnotics/sedatives, which are all drugs of limited benefits to them. Possibly, improvements in living arrangements of AD patients could decrease the necessity for the prescription of psychotropic drugs.

Having comorbidities, such as DM, may also influence the management of patients with dementia. On one hand, our study suggests that DM may accelerate the course of cognitive decline as well as create more possibilities for contact with health care, resulting in an earlier detection and diagnosis of dementia. Likely because physicians may fear the risks of polypharmacy and worsening of DM control, AD patients with comorbid DM were deprived from the prescription of cholinesterase inhibitors and memantine, which are currently the only drugs that could help with their cognition.

4 Part 3: Life-course perspective on brain health

Study 10: Cermakova P, Muller M, Armstrong AC, Religa D, Bryan RN, Lima JAC, Launer LJ. Subclinical cardiac dysfunction and brain health in midlife: CARDIA (Coronary Artery Risk Development in Young Adults) Brain MRI sub-study. Journal of the American Heart Association. 2017;6[26].

Study 11: Cermakova P, Ding J, Meirelles O, Reis J, Religa D, Schreiner PJ, Jacobs DR, Bryan RN, Launer LJ. Carotid intima-media thickness and markers of brain health in a bi-racial middle-aged cohort: CARDIA Brain MRI sub-study. The journals of gerontology. Series A, Biological sciences and medical sciences. 2020;75(2):380-386[134].

Study 12: Cermakova P, Formanek T, Kagstrom A, Winkler P. Socioeconomic position in childhood and cognitive aging in Europe. Neurology. 2018;91:e1602-e1610[133].

Study 13: Cermakova P, Pikhart H, Ruiz M, Kubinova R, Bobak M. Socioeconomic position in childhood and depressive symptoms in later adulthood in the Czech Republic. Journal of Affective Disorders. 2020;272:17-23[135].

4.1 Objectives

The third part of the thesis deals with factors operating decades before older adults manifest with symptoms of cognitive impairment or depression. Study 10 aimed to find out whether subclinical cardiac dysfunction in young adulthood is associated with differences in MRI markers of brain health in mid-life. The objective of Study 11 was to assess the association of subclinical atherosclerosis with MRI indicators of brain health in middle-aged adults. Study 12 examined the association of childhood SEP with the level of cognitive performance and the rate of cognitive decline in older adults, while Study 13 focused on the relation of childhood SEP with depressive symptoms in later adulthood.

4.2 Methods

4.2.1 Participants

Data of participants in the CARDIA study were used in Studies 10 and 11. CARDIA was established in 1985 in 4 centers in the United States (Birmingham, Chicago, Minneapolis and Oakland), aiming to study how cardiovascular diseases develop in young adults[136]. At baseline, participants aged

between 18 and 30 years were randomly selected within race/ethnicity, sex and education strata, contacted by telephone or door-to-door recruiters and invited to take part in examinations in clinics. The original cohort included 5115 persons (mean age 25 years, 52% African Americans, 55% women), who were followed-up in regular intervals for 25 years (Figure 9). At year 25, a sub-sample of 719 individuals (mean age 50 years, 52% women, 39% African American) underwent brain MRI examination at 3 of the CARDIA field centers: Birmingham, Minneapolis and Oakland (CARDIA Brain MRI Sub-study)[137].

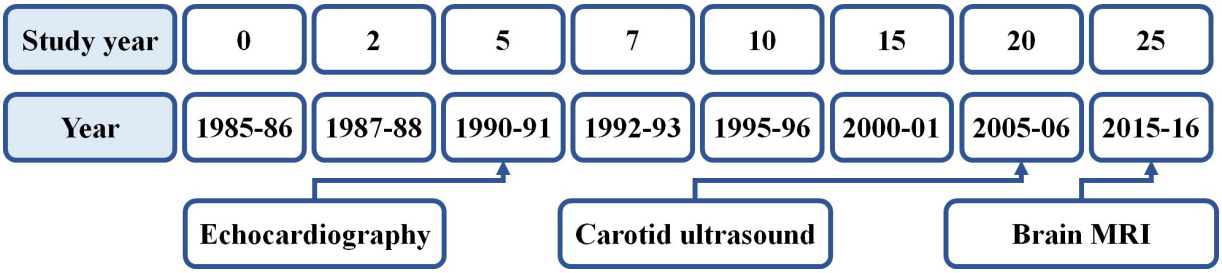

Figure 9 Study years of Coronary Artery Risk Development in Young Adults (CARDIA)

Study 12 used data from the SHARE study. Participants in Study 13 were individuals involved in HAPIEE, which is a longitudinal population-based study initiated in 2002 in order to investigate the effects of traditional as well as non-conventional risk factors for non-communicable diseases in 4 post-communist countries (Czech Republic, Russia, Poland and Latvia)[62]. We used data from the first and second wave conducted in the Czech Republic. The Czech cohort consisted of a random sample of men and women aged 45–69 years at baseline, stratified by sex and 5-year age groups, selected from population registers, residing in 6 towns (Karviná-Havířov, Hradec Králové, Jihlava, Kroměříž, Liberec and Ústí nad Labem). The baseline data collection was conducted in 2002-2004, when participants were visited at home by trained staff and completed a structured interview. A total of 8856 individuals (mean age 58 years, 53% women) took part (response rate 55%) in the first wave of the study. The second wave in 2006-2008 re-examined 5210 individuals (attrition 41%), using CAPI.

4.2.2 Assessment of brain health

The third part of the thesis concerns the following brain outcomes: "MRI markers of brain health" (Studies 10-11), "cognition" (Study 12) and "depressive symptoms" (Study 13). In Studies 10 and 11, brain health was assessed by MRI, performed using 3-T MR scanners located at 3 CARDIA sites

(Siemens 3T Tim Trio/VB 15 platform; Siemens 3T Tim Trio/VB 15 platform and Philips 3T Achieva/2.6.3.6 platform)[24]. Parameters of our interest were: white matter fractional anisotropy (Study 10), cerebral blood flow of gray matter and total brain (Study 11) and volumes of total brain, white matter, gray matter as well as abnormal white matter (both Study 10 and 11).

White matter fractional anisotropy was estimated from diffusion tensor imaging and was a measure of microstructural integrity of the white matter[138]. Cerebral blood flow was measured using pseudo-Continuous Arterial Spin Labeling technique. The mean perfusion (ml/100 g/min) was quantified for the gray matter and the total brain. Total brain volume was estimated as the sum of gray matter and white matter volumes from the sagittal 3D T1 sequence. Abnormal white matter volume reflects mainly white matter hyperintensities and was estimated from the sagittal 3D fluid-attenuated inversion recovery, T1 and T2 sequences. As its distribution was skewed, we categorized it into three groups: none (volume 0 cm^3), little ($\leq$ 0.3 cm^3) and high (>0.3 cm^3).

In Study 12, cognitive functions were assessed for verbal learning, immediate recall and delayed recall. In Study 13, depressive symptoms were assessed with Center for Epidemiological Studies – Depression (CES-D) scale, which is an instrument for measuring depressive symptomatology in the general population[139]. Individuals were asked to rate how often over the past week they experienced 20 different symptoms associated with depression (such as depressed mood, hopelessness, loneliness as well as changes in appetite, concentration, sleep, enjoyment and other factors[139]), with possible response options spanning from 0 (rarely or none of the time) to 3 (most or almost all the time). The total score ranged from 0 to 60, with higher scores indicating greater depressive symptoms. We used a cut-off of 16+ to indicate the presence of depressive symptoms[140, 141].

4.2.3 Other variables

Study 10 focused on markers of subclinical cardiac dysfunction, which included 3 echocardiographic parameters that are known to be predictors of incident heart failure[142-144]: left ventricular ejection fraction, left atrial volume and left ventricular mass. These measures were derived from a two-dimensional and guided M-mode echocardiography, which was acquired at the follow-up year 5. The main predictor in Study 11 was carotid intima-media thickness (cIMT), acquired through ultrasound measurements performed at the follow-up year 20. A composite measure of cIMT was obtained from measurements of the tunica media and intima on the left and right side of the neck in

3 segments of the carotid arteries: the common carotid artery, the carotid artery bulb and the internal carotid artery.

In Studies 12 and 13, the main predictor of interest was childhood SEP. In Study 12 based on SHARE, we used a measure of housing conditions, operationalized by a composite indicator capturing two aspects: 1) crowding, defined as a ratio of number of rooms in the household / number of household members; and 2) number of books at home. We created a variable "socioeconomic hardship", which corresponds to approximately the most adverse 4-5% of the distribution of the composite variable. In addition, we investigated the variable "crowding" by quartiles in order to assess a dose-response relationship. This data come from specific waves that were devoted to collecting information about individuals' life histories (SHARELIFE), using a Life History Calendar[145] in order to improve the recollection process.

In Study 13 based on HAPIEE, childhood SEP was operationalized by housing conditions and parental education. Housing conditions were defined by the number of household amenities the participants had access to in childhood (cold tap water, hot tap water, radio, fridge, own kitchen and own toilet). The participants also reported the highest completed education of their mothers and their fathers, with five possible answers: incomplete primary or no formal education, primary, vocational, secondary (high school diploma), university. As few parents reported to have no formal education, we classified parental education into four categories: primary or lower vs. vocational vs. secondary vs. university.

The analyses of Studies 10 and 11 based on CARDIA were adjusted for CVRFs assessed in clinic (systolic and diastolic blood pressure, BMI, total cholesterol, fasting plasma glucose, smoking and sedentary behavior), self-reported alcohol intake, *APOE* ε4 allele and sociodemographic factors. The analysis of Study 12 based on SHARE was adjusted for sociodemographic and health-related covariates described in previous section. The analysis of Study 13 was adjusted for similar covariates: sociodemographic ones included age, sex, educational attainment, marital status, paid work during the last year, material deprivation score and social isolation. Health-related covariates were smoking status, high frequency of alcohol consumption, obesity, self-reported hypertension, DM or hypercholesterolaemia, cardiovascular disease and cancer.

4.2.4 Statistical analysis

Derivation of analytical samples is presented on Figure 10. In Study 10, we applied linear regression to investigate the association of each echocardiographic parameter (left ventricular ejection fraction, left atrial volume and left ventricular mass) with several outcomes: white matter fractional anisotropy, total brain volume, gray matter volume and white matter volume. We also used multinomial logistic regression to estimate the OR with 95% CI for the association of each echocardiographic parameter with high and low abnormal white matter, relative to no abnormal white matter. The analyses were adjusted for age, sex, ethnicity, education, field center, total intracranial volume as well as CVRFs.

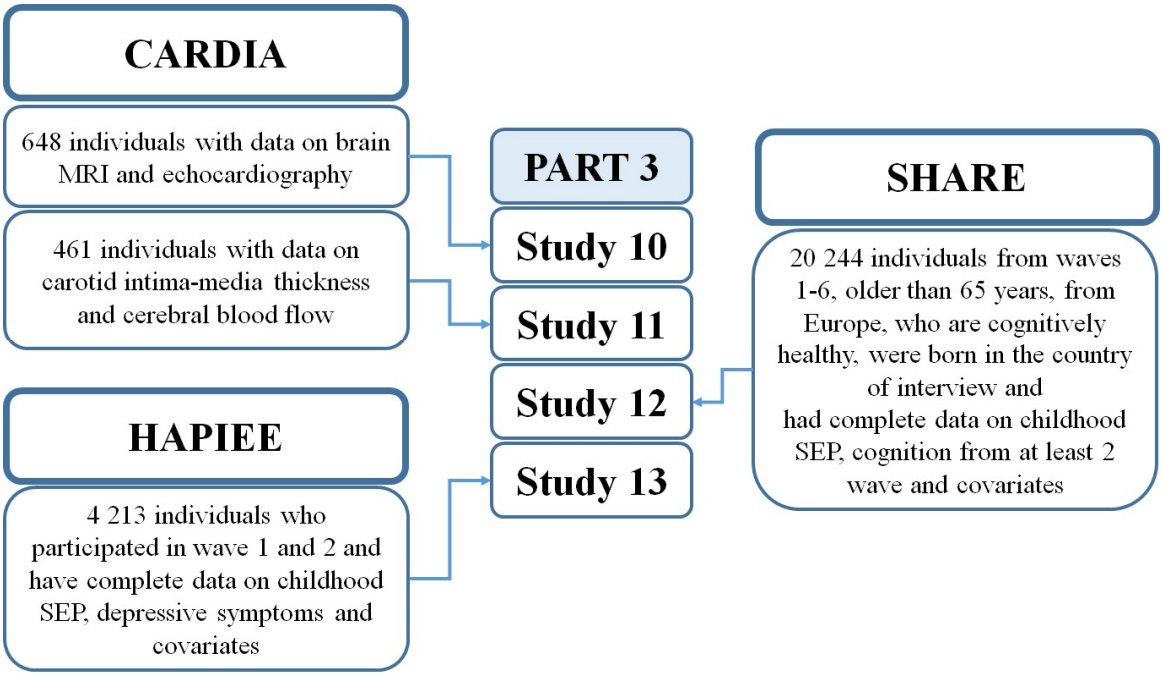

Figure 10 Selection of the analytical samples in Part 3

CARDIA, Coronary Artery Risk Development in Young Adults; HAPIEE, Health, Alcohol and Psychosocial factors In Eastern Europe; SEP, socioeconomic position; SHARE, Survey on Health, Ageing and Retirement in Europe; SveDem, Swedish Dementia Registry

Similar approach was used in Study 11: Linear regression examined the association of cIMT with gray matter and total cerebral blood flow and volumes of gray matter and total brain. Multinomial logistic regression assessed the association of cIMT with abnormal white matter. Covariates were adjusted for in several steps. First, we adjusted for age, sex, ethnicity, education, CARDIA site and total brain volume (models with cerebral blood flow as dependent variable) or intracranial volume

(models with brain volumes as dependent variables). Second, we adjusted for each CVRF separately. In the end, we entered all CVRFs in the final model simultaneously.

In Study 12, linear regression was employed to study the association of socioeconomic hardship / crowding with cognition. Further, we used linear mixed models to assess the relation of childhood SEP to the rate of cognitive decline, with models including time (in years since baseline), childhood socioeconomic hardship and their interaction term. The models were adjusted for sociodemographic and health-related factors. In Study 13, binary logistic regression examined associations of each childhood SEP marker (access to household amenities, mother´s education, father´s education) with depressive symptoms. The ORs were first adjusted for age and sex. Second, we included indicators of current SEP (current education and material deprivation score). Third, we added remaining sociodemographic and health-related covariates.

4.3 Results

4.3.1 Markers of cardiovascular health and brain MRI in mid-life (Studies 10 and 11)

In a sample used for the investigation of subclinical cardiac dysfunction (n=648; 52% women; 38% African Americans), participants were on average 30 years old when they underwent echocardiography and 50 years old when brain MRI was acquired. Left atrial volume was associated with lower white matter fractional anisotropy, when adjusted for all covariates (B=-0.002, 95% CI -0.004; -0.0004; Table 10). There was no statistical interaction with sex or ethnicity, however, analyses stratified by sex/ethnicity showed that this association was present only in men and not in women and in African Americans and not Caucasians. There were no other associations of cardiac parameters with any brain outcomes.

Table 10 Association of left atrial volume with white matter fractional anisotropy; data from Coronary Artery Risk Development in Young Adults (CARDIA) study

	B (95% CI)	
	Model 1	Model 2
All participants	-0.003 (-0.004; -0.001)*	-0.002 (-0.004; -0.0004)*
Caucasians	-0.001 (-0.004; 0.001)	-0.001 (-0.003; 0.001)
African Americans	-0.004 (-0.007; -0.001)*	-0.004 (-0.007; -0.001)*
Women	-0.002 (-0.005; 0.001)	-0.002 (-0.005; 0.001)
Men	-0.003 (-0.006; -0.001)*	-0.003 (-0.005; -0.0003)*

CI, confidence interval; *p<0.05

Results are derived from linear regression and indicate B for the association of left atrial volume (per standard deviation, as it was modelled as a z-score) with white matter fractional anisotropy.

Model 1: adjusted for age, sex (not models stratified by sex), ethnicity (not models stratified by ethnicity), field center, years of education, intracranial volume
Model 2: also adjusted for systolic blood pressure, diastolic blood pressure, body mass index, total cholesterol, fasting plasma glucose, smoking status, sedentary time, alcohol intake, APOE ε4 allele

In a sample used for the investigation of cIMT (n=461; 54% women; 34% African Americans), participants were on average 46 years old when cIMT was measured and 51 years old when the brain MRI was acquired. Higher cIMT was associated with lower gray matter cerebral blood flow (B=-1.36; 95% CI -2.67 to -0.05) and lower total cerebral blood flow (B=-1.26; 95% CI -2.44 to -0.08), adjusting for age, race, sex, years of education, CARDIA field center and total brain volume (Table 11). The association of cIMT with the cerebral blood flow became non-significant when we

controlled for CVRFs. Adjusting for them separately, the variables that attenuated the associations the most were blood pressure, BMI and fasting blood glucose. Controlling for all CVRFs together, the association lost statistical significance (gray matter cerebral blood flow: B=-0.77; 95% CI -2.21 to 0.67; total cerebral blood flow: B=-0.83; 95% CI -2.13 to 0.47). CIMT was not associated with any other brain outcomes.

Table 11 Association of carotid intima-media thickness with cerebral blood flow; data from Coronary Artery Risk Development in Young Adults (CARDIA) study

	Gray matter cerebral blood flow	Total cerebral blood flow
Model 1	-1.36 (-2.67; -0.05)*	-1.26 (-2.44; -0.08)*
Model 2	-0.90 (-2.28; 0.48)	-0.87 (-2.12; 0.38)
Model 3	-1.01 (-2.33; 0.32)	-0.95 (-2.15; 0.25)
Model 4	-0.90 (-2.24; 0.44)	-0.89 (-2.10; 0.32)
Model 5	-1.21 (-2.55; 0.13)	-1.13 (-2.34; 0.08)
Model 6	-1.07 (-2.40; 0.26)	-1.03 (-2.24; 0.17)
Model 7	-1.39 (-2.70; -0.08)*	-1.29 (-2.48; -0.11)*
Model 8	-1.37 (-2.68; -0.06)*	-1.30 (-2.49; -0.12)*
Model 9	-0.77 (-2.21; 0.67)	-0.83 (-2.13; 0.47)

*p<0.05; results are B coefficients with 95% confidence intervals for the association of carotid intima-media thickness (per standard deviation) with cerebral blood flow, derived from linear regression

Model 1: adjusted for age, sex, race, CARDIA site, years of education and total brain volume
Model 2: adjusted for covariates in Model 1 and cumulative exposure to systolic blood pressure
Model 3: adjusted for covariates in Model 1 and cumulative exposure to diastolic blood pressure
Model 4: adjusted for covariates in Model 1 and cumulative exposure to body mass index
Model 5: adjusted for covariates in Model 1 and cumulative exposure to total blood cholesterol
Model 6: adjusted for covariates in Model 1 and cumulative exposure to fasting plasma glucose
Model 7: adjusted for covariates in Model 1 and smoking status
Model 8: adjusted for covariates in Model 1 and sedentary behavior
Model 9: adjusted for all covariates in Model 1-8

Cumulative exposure to covariates in Model 2-6 were calculated as area under the curve from baseline up to follow-up year 20

4.3.2 **Childhood poverty and brain health** (Studies 12 and 13)

In a sample used to investigate the association of childhood SEP with cognition (n=20 244, median age at baseline 71 years old; 54% women), childhood socioeconomic hardship was associated with a lower baseline level of performance in all cognitive tests, even when adjusted for all covariates (Table 12). Childhood socioeconomic hardship was not related to the rate of cognitive decline over time. Crowding in childhood, analyzed as a continuous variable, was associated with lower baseline level of cognitive performance. When analyzed by quartiles, there was a dose-response pattern. Crowding was not associated with the rate of cognitive decline over time.

Table 12 Association of childhood socioeconomic hardship with baseline level of cognitive performance and rate of cognitive decline; data from Survey of Health, Ageing and Retirement in Europe (SHARE)

	Model 1	Model 2
A) Level of cognitive performance		
Verbal fluency	−0.26 (−0.32; −0.20)**	−0.15 (−0.21; −0.09)**
Immediate recall	−0.29 (−0.36; −0.23)**	−0.16 (−0.22; −0.10)**
Delayed recall	−0.27 (−0.33; −0.21)**	−0.14 (−0.20; −0.08)**
Global cognition	−0.27 (−0.32; −0.23)**	−0.15 (−0.20; −0.10)**
B) Rate of cognitive decline		
Verbal fluency	0.02 (−0.05 to 0.08)	-
Immediate recall	0.01 (−0.01 to 0.03)	-
Delayed recall	0.00 (−0.03 to 0.02)	-
Global cognition	0.00 (−0.01 to 0.01)	-

A) Results are unstandardized B coefficients with 95% confidence intervals for the association of childhood socioeconomic hardship with the baseline level of cognitive performance; derived from linear regression.

Model 1: adjusted for age, sex, country of origin.
Model 2: adjusted also for education, cardiovascular disease, body mass index, physical inactivity, depressive symptoms, alcohol, smoking, partner in household, working at present
**p<0.001

B) Results are B coefficients with 95% confidence intervals for the interaction childhood socioeconomic hardship x time since baseline; derived from linear mixed-effects models

Model 1: age at baseline, sex, time (since baseline), childhood socioeconomic hardship, interaction of time and childhood socioeconomic hardship and country of origin.

In the sample used to investigate the relationship between childhood SEP and depressive symptoms in later adulthood (n=4 213 individuals; mean age 58 years; 54% women), higher access to household amenities and higher education of both mother and father were all associated with lower odds of depressive symptoms, adjusting for age and sex (Table 13). After adjustment for indicators of current SEP, the ORs attenuated, but the associations remained statistically significant for household amenities (p for trend 0.04) and borderline statistically for mother´s education (p for trend 0.05). However, the ORs for the association of father´s education with depressive symptoms became close to unity after accounting for current SEP. Adjusting for remaining sociodemographic and health-related covariates attenuated all associations that did not persist to be statistically significant (not presented in this thesis).

Table 13 Associations of indicators of childhood socioeconomic position with depressive symptoms; data from Health, Alcohol and Psychosocial factors In Eastern Europe (HAPIEE) study

	Model 1	p for trend	Model 2	p for trend
Access to household amenities				
Lowest	Reference		Reference	
Lower	0.88 (0.65; 1.18)		0.93 (0.69; 1.27)	
Higher	0.70 (0.53; 0.91)	<0.001	0.79 (0.60; 1.05)	0.04
Highest	0.62 (0.46; 0.83)		0.76 (0.56; 1.03)	
Father´s education				
Primary or lower	Reference		Reference	
Vocational	0.80 (0.66; 0.99)	0.03	0.88 (0.71; 1.09)	0.82
Secondary	0.73 (0.56; 0.93)		0.89 (0.68; 1.17)	
University	0.77 (0.54; 1.11)		1.06 (0.72; 1.57)	
Mother´s education				
Primary or lower	Reference		Reference	
Vocational	0.75 (0.62; 0.90)	<0.001	0.86 (0.70; 1.05)	0.05
Secondary	0.69 (0.53; 0.91)		0.84 (0.63; 1.12)	
University	0.34 (0.12; 0.94)		0.44 (0.16; 1.22)	

Results are odds ratios with 95% confidence intervals for the associations of each indicators of childhood socioeconomic position (modelled separately) with depressive symptoms.

Model 1: adjusted for age and sex
Model 2: adjusted for age, sex and indicators of current socioeconomic position (current education and material deprivation score)

4.4 Discussion

Studies presented in the third part of the thesis took a life-course approach to understanding brain health. We found that subclinical cardiac dysfunction indicated by a higher left atrial volume in young adults – only 30 years old – predicted a subtle injury of white matter integrity in the brain 20 years later. Middle-aged individuals with higher markers of subclinical carotid atherosclerosis had lower brain perfusion. When examining the lifecourse influence of childhood exposures, we found that childhood SEP was associated with a lower level of cognitive performance, however, it was unrelated to the speed the cognitive functions declined over time. Lower childhood SEP was also associated with depressive symptoms in later adulthood. While access to household amenities in childhood and mother´s education predicted depressive symptoms independently of current SEP, the relationship between father´s eduction and one´s depressive symptoms were largely explained by own socioeconomic status.

The association of subclinical cardiac dysfunction with low white matter integrity is in line with evidence of a strong relationship between heart failure and risk of brain disorders, such as dementia[146]. Here we suggest that cardiac function in as soon as young adulthood may influence brain health later, even extending the effects of traditional CVRFs. Previous studies suggest that African Americans are disproportionately burdened by heart failure and dementia[36, 147]. The present study indicates that particularly young African American men may be at risk for compromised brain health due to cardiac dysfunction. As enlarged left atrium is associated with previous chronic exposures to CVRFs, especially elevated blood pressure and obesity[142], we propose that interventions aiming at their reduction in order to improve cardiac function may also benefit brain health. Possibly, African American men can have the largest benefit from such interventions.

The association of cIMT with lower brain perfusion is in accordance with a number of studies that emphasize the involvement of atherosclerosis in the development of brain disorders, such as dementia[148]. We showed that lower brain perfusion may be present already in mid-life in the terrain of vessels changed by atherosclerosis. While atrophy and white matter hyperintensities may represent more advanced pathologies, which occur later during the life-course, lower brain perfusion may be an early marker of abnormal brain aging[24]. The association between cIMT and lower cerebral blood flow was modest in the middle-aged population, but may be clinically relevant. Al Hazzouri found that cIMT is related to lower cognitive functioning in this middle-aged cohort[149]. The

association is consistent with the link between increased cIMT and future risk of dementia[150] as well as the relation between lower brain perfusion in mid-life and occurrence of dementia later in life[151]. It may be indicative of subtle vascular pathologies already in middle-aged adults that will proceed to accumulate into old age and possibly form the structural basis for dementia. Early identification and intervention to delay cardiovascular risk factors may possibly modulate the trajectory of cerebral blood flow as people age and develop brain pathology.

In line with previous epidemiological studies[69-75] as well as animal experiments[152, 153], we demonstrated that the roots of cognitive ability in old age may be influenced by resources the individuals were exposed to while growing up. Favourable childhood socioeconomic environment contributes to better cognitive skills throughout the lifespan, supporting the construct of passive cognitive reserve. However, benefits stemming from high childhood SEP are unlikely to affect active cognitive reserve by counteracting accumulating age-related pathology in order to slow down the rate of cognitive decline. Thus, we suggest that interventions aimed to improve cognitive aging in old age should decrease socioeconomic hardship in childhood. The effects of adverse socioeconomic conditions in childhood may be mitigated by reductions in several risk factors, especially by providing opportunities of education to individuals who have experienced the strongest socioeconomic adversities.

The socioeconomic environment in which people grew up may also have long-lasting effects on depressive symptoms in later adulthood. Material deprivation in childhood, as captured by access to household amenities, could exhibit long-lasting effects on adult mental health even through mechanisms independent from how adult socioeconomic circumstances shape the risk of depressive symptoms. Some authors suggest that the link between low parental education and poor mental health of their offsprings largely exists because parents with higher education tend to have children that reach a higher SEP in adulthood, which contributes to their depressive symptoms[154]. However, this was more apparent for father´s education than mother´s. Increased educational opportunities, in particular for women, could significantly contribute to breaking the chain of intergenerational cycle of low SEP and poor mental health.

5 Methodological considerations

Results of the presented studies need to be interpreted in the context of the used methodology. Errors that occurred while performing the studies may have jeopardized the accuracy of our estimates. The estimates are accurate if they are precise as well as valid. Random errors are a threat to precision, systematic errors may result in bias, which decreases the validity of the results. While the risk of random error decreases with higher sample size, bias cannot be eliminated by increasing the number of participants. As the sample sizes used in all the studies were large, the precision of the study results is considered fairly high, with the exceptions of some sub-group analyses. On the contrary, bias likely occurs in all presented studies. Three main sources of bias are confounding, selection bias and misclassification and may result in overestimation or underestimation of the parameters of interest.

The only possible way to eliminate confounding is randomization in experimental design. All the presented studies in this thesis are observational, thus confounding appears in all of them. The analyses were adjusted for a number of confounding factors, however, residual confounding by factors, which were not measured or were not measured optimally can´t be eliminated. Selection bias also likely appears in all presented studies. Even though random sampling was used in all population-based cohorts (CZEMS, SHARE, CARDIA, HAPIEE), the decisions of individuals to agree to take part in a research are not random. Usually, men of lower socioeconomic status, who are exposed to multiple risk factors, are less likely to participate in research, and are also more likely to be lost to follow-up[155]. In addition, results of the four population-based cohorts can be generalized only to community-dwelling individuals. Overall, this generally implies that the burden of brain disorders is likely underestimated in all studies based on these four cohorts.

The register-based studies likely face a risk of selection bias as well. It is estimated that only 30-40% of incident dementia cases are captured in SveDem[156]. It is not known how patients with dementia who are registered differ from those who are not, however, an examination of another Swedish quality registry indicated that individuals who appeared in a quality registry were more likely to be men, have a higher socioeconomic status and be in general healthier[157]. If this holds for SveDem, it may be speculated that the gap in the management of patients with dementia is underestimated.

The structure and function of the brain was assessed using a variety of methods on different levels of complexity, ranging from simple screening instruments, through clinical diagnosis to a state-of-

the-art brain MRI. A limitation using brief cognitive tests and scales on depressive symptoms, such as EURO-D or CES-D is their unknown clinical relevance. The diagnoses of dementia used in the register-based studies reflect the reality in clinical settings, however, their validity has not been examined. A particular concern is differential misclassification of childhood SEP, which has been retrospectively collected and may possibly contribute to overestimation of the associations of childhood SEP to later-life markers of ill brain health.

6 Ethical issues

Health-related research involving humans is ethically justified if it has scientific and social value, meaning that it should generate new knowledge that facilitates protection and promotion of health[158]. The WHO defines research with human subjects as any activity that entails systematic collection or analysis of data with the aim to generate new knowledge, in which humans are either (1) exposed to manipulation, intervention, observation, or other interaction with investigators either directly or through alteration or their environment; or (2) become individually identifiable through investigator´s collection, preparation, or use of biological material or medical or other records[159].

Research ethics governs standards of how to protect the autonomy and personal integrity of research participants. Autonomy relates to the right of everyone to make their own decisions. Personal integrity comprises privacy, dignity and presupposes respect for other people´s feelings. In the studies included in this habilitation thesis, research participants have been exposed to observation and became individually identifiable through collection of new data as well as the use of medical records. Data collected in these studies largely concerned health, which is considered as sensitive data. Sensitive data is protected by secrecy and requires ethical vetting. In order to maintain people´s autonomy and personal integrity while performing research on sensitive data, an informed consent is usually required.

CZEMS (Studies 1-3) has been approved by the Ethics Committee of the National Institute of Mental Health in Klecany, Czech Republic. Participants have been informed about the purpose of the study and provided an informed consent. SHARE (Studies 4-7 and 12) have been repeatedly reviewed and approved by the Ethics Committee of the University of Mannheim. All participants signed an informed consent. The HAPIEE (Study 13) was approved by the ethics committees at University College London, UK and the National Institute of Public Health in Prague, Czech Republic. All participants gave an informed consent. The analyses based on SHARE and HAPIEE presented in this thesis were also approved by the Ethics Committee of the National Institute of Mental Health in Klecany, Czech Republic.

In Studies 10 and 11 based on CARDIA, all participants provided an informed consent at each exam, and the institutional review board from each participating institution annually approved the CARDIA study. For the CARDIA Brain MRI Sub-study, separate approval was given by the institutional

review boards of the participating sites and by the institutional review boards covering intramural research at the National Institute of Aging in Bethesda, Unites State of America. Separate participant consents in writing for the CARDIA Brain MRI Sub-study were obtained.

Studies 8 and 9 were approved by the regional ethical review board in Stockholm, Sweden and are ethically different from the population-based cohort due to two main reasons: First, no informed consent is acquired for register-based research; second, the research was performed on individuals with dementia, who belong to vulnerable groups of population. Unlike nationwide Swedish health registers (the Swedish Patient Register and Swedish Prescribed Drug Register), participation in quality registers such as SveDem is voluntary and patients´ data can be removed, should they require it. Even though most patients in Sweden are diagnosed and registered to SveDem at a relatively early stage of dementia when their cognitive abilities enable making decisions, it needs to be acknowledged that during the progression of dementia, their capacity to reach decisions (such as a decision to have their data removed from a register) declines.

As categorical exclusion from research may exacerbate health disparities, everybody should be provided appropriate access to participation in research, including underrepresented groups and individuals who cannot give consent[158]. When it is not feasible to obtain the informed consent of the participants (which is the case for register-based research), it is advised that the research procedures that offer no individual benefit pose only minimal risks of discomfort[158]. A justification of performing register-based research is that the imposed risks to harm the participants are small. To reduce the potential harm of utilizing sensitive personal information, data were pseudo-anonymized (which means that the personal identifier was re-coded and the researchers do not have a key to link the data to the individual) and results are presented only at a group level.

7 Summary of main findings

- Alcohol use disorders are the most common brain disorders in the Czech Republic. Their prevalence needs to be reduced.
- Most individuals that show symptoms of mental disorders in the Czech Republic do not utilize mental health care. This large treatment gap needs to be decreased.
- Cognitive and affective health of older adults residing in the Czech Republic seems to be better in recent cohorts. Even larger improvements could be possible.
- Brains of older adults in Scandinavia and Western Europe are healthier compared to their counterparts in Southern Europe and CEE. Targeting modifiable sociodemographic and health-related risk factors may have a particular benefit for the brain health of individuals in Southern Europe and CEE.
- Patients with dementia who live alone or have comorbid DM receive a lower intensity of diagnostics and treatment. Living situation or comorbidities should not be strong barriers to the treatment of AD patients with cholinesterase inhibitors.
- Exposures to cardiovascular risk factors during young adulthood may leave marks on the structure and function of the brain in mid-life. Reduction in cardiovascular risk factors is necessary early in life to protect brain health.
- The roots of brain health of older adults begin in early life in part through childhood socioeconomic conditions. Prevention of childhood poverty and mitigation of risk factors over the whole life-course is needed to protect brain health in older age.

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Appendix

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5. Kucera M, Wolfova K, **Cermakova P**. Changes in depressive symptoms of older adults in the Czech Republic. Journal of Affective Disorders. 2020; 261:139-144[92]. Current impact factor: 4.1 (Study 5)
6. Horackova K, Kopecek M, Machu V, Kagstrom A, Aarsland D, Motlova LB, **Cermakova P**. Prevalence of late-life depression and gap in mental health service use across European regions. European psychiatry : the journal of the Association of European Psychiatrists. 2019;57:19-25[108]. Current impact factor: 3.9 (Study 6)
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11. **Cermakova P**, Ding J, Meirelles O, Reis J, Religa D, Schreiner PJ, Jacobs DR, Bryan RN, Launer LJ. Carotid intima-media thickness and markers of brain health in a bi-racial middle-aged cohort: CARDIA Brain MRI sub-study. The journals of gerontology. Series A, Biological sciences and medical sciences. 2020;75(2):380-386[134]. Current impact factor: 4.7 (Study 11)
12. **Cermakova P,** Formanek T, Kagstrom A, Winkler P. Socioeconomic position in childhood and cognitive aging in Europe. Neurology. 2018;91:e1602-e1610[133]. Current impact factor: 8.7 (Study 12)
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