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INVESTIGATION OF RISK FACTORS IN DIFFERENT SPECTRUMS OF COGNITIVE DECLINE

PhD thesis

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LIST OF ABBREVATIONS

ACE	Addenbrooke's Cognitive Examination
AD	Alzheimer’s disease
AED	antiepileptic drug
AgeCoDe	Ageing, Cognition, and Dementia
ANU-ADRI	Australian National University - Alzheimer's Disease Risk Index
ARB	angiotensin receptor blocker
BDI-II	Beck Depression Inventory II
BMI	body mass index
BPSD	behavioural and psychological syndromes in dementia
CAIDE	Cardiovascular Risk Factors, Aging, and Incidence of Dementia
CDT	Clock-drawing test
CI	confidence interval
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
CT	computed tomography
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5
EEG	electroencephalogram
FDG	fluorodeoxyglucose
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
HC	healthy controls
Hz	hertz
HIV	human immunodeficiency virus
IU	international unit
LIBRA	Lifestyle for Brain Health
MCI	mild cognitive impairment
MoCA	Montreal Cognitive Assessment
MMSE	Mini–Mental State Examination
MRI	magnetic resonance imaging
NCD	neurocognitive disorders

NIA-AA	National Institute of Aging- Alzheimer's Association
NPH	normal pressure hydrocephalus
NPS	neuropsychological
NREM	non-rapid eye movement
OR	odds ratio
PET	positron emission tomography
QoL	quality of life
GLM	general linear model
REM	rapid eye movement
RR	relative risk
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
S1	sleep stage 1
S2	sleep stage 2
S3	sleep stage 3
SCC	subjective cognitive complaints
SCD	subjective cognitive decline
SD	standard deviation
SEA	subclinical epileptiform activity
SPECT	single photon emission computed tomography
SPSS	Statistical Package of Social Science
SSRIs	selective serotonin reuptake inhibitors
STAI	Spielberger State and Trait Anxiety Inventory
VLOM	Verbal-Language/Orientation-Memory
WHO	World Health Organization

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1. INTRODUCTION

1.1. Significance and epidemiology of cognitive decline

Diseases that cause cognitive decline in old age not only affect individuals and their families, but also place an increasing health, social and economic burden on society (1-3).

Nearly 55 million people in the world suffer from dementia (major neurocognitive disorder) and it is estimated that this number could rise to 139 million by 2050 (4, 5). Thus, diseases causing dementia are expected to be the main cause of mortality and morbidity in older people, making dementia and related care a major challenge for society in the coming decades (6).

In Europe, in line with economically developed societies, while the age-specific incidence of dementia is decreasing, a further increase in the number of people with dementia is predicted due to the increasing proportion of elderly people in the population (7).

In Hungary, there is no available dementia register, therefore Hungarian epidemiological data are incomplete. According to various calculation methods and estimates, the number of dementia patients is about 140-250 thousand (8, 9).

1.2. Symptoms of cognitive decline

Dementia is an umbrella term for a clinical syndrome characterized by deterioration in high order cognitive processes (4).

In addition to cognitive deficit, behavioural and psychological symptoms of dementia (BPSD) (aggression, agitation, hallucinations, anxiety, depression, apathy, etc.) and other physical and neurological abnormalities (gait, speech and sleep disorder, incontinence, etc.) are often associated, partly as lobe syndromes. The wide range of clinical presentations of cognitive decline are summarized in **Table 1.**

Table 1. The main clinical signs of cognitive decline. (10)

Cognitive impairment / lobe symptoms
Short/long term memory impairment or amnesia
Learning disability
Complex attention deficit
Disturbance of executive functions: decision-making, judgement
Language dysfunction: anomia, semantic deficit
Disorder of orientation (spatial-visual perception and cognition)
Aphasia, apraxia, agnosia, alexia, agraphia
Behavioural and psychological symptoms (BPSD)
Affective symptoms: anxiety, depression, apathy, euphoria
Psychotic symptoms: hallucinations, delusions, misidentifications
Restlessness: agitation, aggressiveness, nocturnal wandering,
Inhibition, aimlessness, social isolation, paranoia, personality changes
Other abnormalities
Motor abnormalities: postural, gait, bedriddenness
Autonomic abnormalities: incontinence
Sleep disturbance: altered sleep-wake cycles, REM disturbance
Parkinsonism, myoclonus, epilepsy, dysarthria, dysphagia

In patients with dementia, neuropsychological tests can be used to objectify the extent to which cognitive functions expected with age and level of education are impaired. The clinical picture is characterized by a persistent and progressive decline, which prevents the patient from leading an independent daily life. The patient's impaired thinking is not caused by delirium or other mental disorder (e.g., depression or schizophrenia) (11).

The manual, that contains the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-5) criteria (12) used since 2013, introduced the term neurocognitive disorders (NCD), which includes any disorder in which the underlying impairment affects cognitive functions and features deterioration from a previous level. Two levels of severity are distinguished: major and mild neurocognitive disorder. The former has replaced the often-stigmatized term dementia, while the latter succeeded mild cognitive impairment. The six cognitive domains studied are: complex attention, executive functions, learning and memory, language skills, visual perception and construction, and social cognition. Within major neurocognitive impairment, mild, moderate, and severe subtypes are distinguished. The condition can be preceded by asymptomatic but biomarker-positive cases as part of the cognitive continuum. (13).

1.3. Diseases associated with cognitive decline

The group of symptoms can be caused by a wide range of diseases, about 100 of which are currently known. The risk and symptoms of developing dementia are significantly influenced by different associated pathological processes, frequently referred as co-pathology such as vascular ethology (14).

The main cause of dementia in old age is Alzheimer's disease (AD) (15). AD is the most common neurodegenerative disease (16). The exact mechanism of AD development is not known, but a combination of factors alters the metabolic processes in the brain. In addition to cerebral vascular dysfunction, microbleeds appear, inflammation develops by activating microglial processes, lipid transporters are altered, and amyloid clearance mechanisms are also impaired. These result in the deposition of amyloid plaques between the neurons and hyperphosphorylated tau tangles in the neurons (17). The appearance of the two proteins is different in time and space. The amyloid appears earlier in the disease, primarily in the mesolimbic areas, hippocampus and basal forebrain, and then gradually affects the entire cortex. The tau appears later in the disease, typically in the transentorhinal cortical areas, then in the limbic areas, and finally in the neocortex (18). According to neuropathologic studies, amyloid plaque is neurotoxic, degenerates synaptic connections, lowers neuronal survival, increases oxidative stress, causes inflammatory changes, destabilizes the neural network and can generate epileptiform discharges (19, 20). The first symptoms typically appear around the age of 65, with a disease course of about 4-8 years, but this can vary considerably, as can the dominant symptoms. In 2018 the research framework of the National Institute on Aging and the Alzheimer's Association (NIA-AA) defines Alzheimer's disease in biological terms, based on neuropathological changes or biomarkers, and considers cognitive impairment as a sign of the disease, rather than a definition of it (13).

Alzheimer's disease is responsible for two-thirds of dementia cases in people over 65, followed by vascular dementia, mixed dementia, Lewy body dementia and frontotemporal dementia (21, 22). In secondary dementias, treating and eliminating the underlying cause can reduce symptoms and improve the patient's condition (23). **Table 2.** shows the most common pathologies that cause cognitive decline.

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Table 2. Etiological classification of the most common pathologies causing cognitive decline. (Based on the Neurology textbook of Szirmai 2017.) (10, 11)

Primary degenerative diseases
Alzheimer's disease
Frontotemporal lobar degeneration
Parkinson's disease
Diffuse cortical Lewy body disease
Progressive supranuclear palsy
Corticobasal degeneration
Huntington's disease
Cerebrovascular diseases
Lacunar encephalopathy
Multiinfarct dementia
Transient global ischaemia
Strategic infarcts
Infectious diseases
Viral encephalitis
Bacterial meningitis
Neurosyphilis
Human immunodeficiency virus (HIV)
Prion and slow viral diseases
Metabolic diseases
Diabetes mellitus
Hypothyroidism
Hepatic encephalopathy
Dialysis dementia
Deficiency diseases
Vitamin B12 deficiency
Folic acid deficiency
Wernicke-Korsakov encephalopathy (vitamin B1)
Pellagra encephalopathy (vitamin B3)
Others
Brain tumours
Normal pressure hydrocephalus (NPH)
Trauma
White matter disorders
Medication related

1.4. Different spectrums of cognitive decline

The development of dementia can take several decades, the progress of cognitive decline is demonstrated by **Figure 1.** (24).

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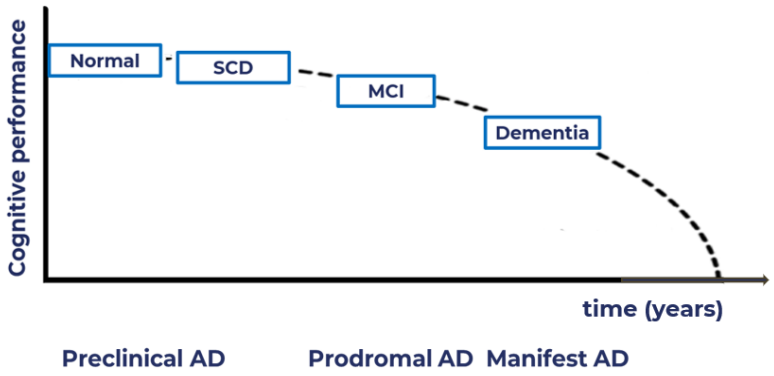

Figure 1. Depicted is the course of cognitive decline in relation to progressive disease pathology in Alzheimer's disease. (Based on Jessen et al., 2014.) (24)
AD: Alzheimer's disease, MCI: mild cognitive impairment, SCD: subjective cognitive decline.

Dementia is often preceded by mild cognitive impairment (MCI), in which the cognitive deficit does not yet interfere with independence in daily activities, but requires more effort, a compensatory strategy – thus the diagnostic criteria for dementia are not yet met – but the cognitive deficit is already detectable by neuropsychological tests sensitive to it (25). The heterogeneity of the patient population raised the need for subgroup formation. MCI may be amnestic or non-amnestic, or may affect one or more areas (26). Amnestic MCI is twice as common as non-amnestic MCI. Several studies have shown that the separation of subgroups can be of practical importance regarding progression (27, 28). The clinical relevance of mild cognitive impairment is that the annual dementia conversion rate in this condition is 10-15% instead of the 1-4% rate of the average population (29).

Subjective cognitive complaints (SCC) is a self-reported experience of persistently impaired cognitive functions (e.g., memory, visuospatial skills, language functions). SCC is an integral component of the diagnostic criteria of MCI (30) and also a key hallmark of subjective cognitive decline (SCD), where individuals show a normal performance on standardized cognitive tests (24). The usefulness of the SCC in predicting cognitive decline shows ambiguous results in a short time interval, because of the possible overreporting of the SCC in individuals with higher levels of anxiety or mood problems (31). In addition, a large longitudinal autopsy study has confirmed the long-term

prognostic significance of SCC by showing that subjective complaints occur more than nine years before the diagnosis of MCI (32). Further research has validated these findings, particularly in the SCC population with chronic cardiovascular disease (33).

In case of SCD before the diagnostic criteria for MCI are met, the patients may perceive cognitive decline, but neuropsychological tests cannot yet objectify the cognitive decline (24). There is increasing evidence that SCD can be the first symptomatic manifestation of AD (34). Although the majority of patients with subjective memory impairment are not expected to develop dementia, they are at twice the relative risk of developing MCI or dementia compared to those without SCC (35). The literature cites factors that increase the risk of cognitive decline as SCD plus criteria: memory decline independent of other cognitive domains, onset of symptoms within 5 years, onset of symptoms at age 60 or older, concern about memory decline, persistence of SCD over time, seeking medical help, confirmation of cognitive decline by an outside observer. It describes reversible, stable, and progressive subtypes. The reversible subtype is often caused by psychiatric pathologies, drug effects or side effects. The stable subtype might occur during normal ageing, while the progressive form might be the first clinical manifestation of neurodegenerative diseases associated with dementia (34). SCC and SCD are not mentioned as a diagnostic category of DSM-5 or International Classification of Diseases-11.

1.5. Treatment options of cognitive decline

Around 80% of dementia-related diseases have no cure, but the progression of the disease can be slowed down, giving patients and their relatives a better quality of life (36). There are more than a hundred drug trials around the world, but so far there has been little therapeutic success (37). If the cause of the disease cannot be treated, starting progression-slowing medication as early as possible may provide the most benefit (38).

Current scientific opinion suggests that a reduction in the prevalence of dementia can be expected from the development and implementation of various dementia prevention strategies, as the onset of the disease could be prevented in more than a third of cases (39). The EU-FINGERS Consortium, bringing together leading European researchers, aims to improve the prevention of dementia and Alzheimer's disease and to develop joint European research programs and clinical guidelines (40).

1.6. Primary prevention of cognitive decline

Primary prevention aims to reduce the risk of developing dementia (by reducing the number of risk factors) through patient education and health education.

There are many known risk factors for cognitive decline. Like cardiovascular risk factors, some of these cannot be modified (age, sex, genetic factors). Ageing is one of the most important risk factors for developing dementia: Over 65, the risk of dementia doubles every 5 years (41). Alzheimer's disease, which accounts for nearly two-thirds of dementias, affects women twice as often as men. Genetic factors are of particular importance in the development of dementia with early onset and familial accumulation (42). Modifiable risk factors of dementia include lower education level, high blood pressure, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, social isolation, excessive alcohol consumption, head injury with loss of consciousness, air pollution. By reducing these 12 risk factors, the onset of dementia could be prevented or delayed in nearly 40% of cases. The relevance of the modifiable risk factors in the reduction cognitive decline is shown in **Table 3.** (43).

Table 3. Relevance of the modifiable risk factors in the reduction of cognitive decline at different life periods. (Based on Livingston 2020) (43)

Life periods	Modifiable risk factors	Relevance
Early life	Less education	7%
Midlife	Hearing loss	8%
	Traumatic brain injury	3%
	Hypertension	2%
	Alcohol consumption	1%
	Obesity	1%
Later life	Smoking	5%
	Depression	4%
	Social isolation	4%
	Physical inactivity	2%
	Air pollution	2%
	Diabetes	1%

Several studies have shown that regular cognitive training, physical activity, social activity, Mediterranean diet, adequate quality and quantity of sleep and mood balance can help to prevent cognitive decline (44-48).

In addition to improving patients' health awareness, the prevention and treatment of cardiovascular and metabolic diseases can also reduce the risk of developing dementia. Treating hypertension reduces the risk of dementia and cognitive decline. Angiotensin II receptor blockers (ARBs) (49, 50) and dihydropyridine-containing calcium channel blockers have been shown to be the most effective drug classes (51). The mid- to long-term use of statins for cognitive decline and dementia is not yet clear (52, 53). The neurocognitive impacts of diabetes mellitus type 2 suggest to a notable acceleration of natural brain aging (54). Diabetes mellitus is a risk factor not only for vascular dementia but also for Alzheimer's disease. The mechanism is not clear but is presumably multifactorial. Optimal management of diabetes risk factors early in life may be important in preventing late-onset dementia (55).

It is not yet clear which factors play a more significant role in the development, course, and progression of the disease at the level of the individual. Longitudinal studies that look beyond the traditional risk factors may provide a solution to a more complex understanding of the problem. It is advised that the research approach be standardized and coordinated internationally (56).

The Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) Risk Score was the first validated tool for estimating the risk of later developing dementia in middle-aged people (57). It considers age, sex, education, systolic blood pressure, body mass index, total cholesterol, physical activity and APOEε4 status and predicts the risk of developing dementia 20 years later.

By focusing on modifiable, lifestyle-related risk factors, Lifestyle for Brain Health (LIBRA) may assist in identifying and monitoring risk status in dementia-prevention programs. LIBRA score consists of 9 modifiable risk and 3 protective factors. Coronary heart disease, diabetes, high cholesterol, high blood pressure, depression, obesity, smoking, physical inactivity, and renal illness are risk factors. Low-to-moderate alcohol consumption, strong cognitive activity, and a healthy diet are protective factors. Each factor is weighted according to its relative risk (58). In addition to predicting cognitive impairment and a decline in information processing speed over a 12-year period, LIBRA also predicted individual risk of dementia over a follow-up period of up to 16 years. LIBRA can help develop innovative strategies to prevent dementia by focusing on

modifiable risk factors, for example by raising awareness of the opportunities to reduce the risk of dementia in middle age and by focusing on lifestyle changes (59).

The Australian National University - Alzheimer's Disease Risk Index (ANU-ADRI) is an evidence-based validated tool developed in Australia based on systematic review of evidence of risk factors associated with an increased risk of developing AD, over the age of 60 years (60). Dementia Screening Indicator is a simple tool, based on four cohorts, developed to screen people in primary care settings to identify high-risk patients who need further cognitive testing (61). Ageing, Cognition, and Dementia (AgeCoDe) Prediction Score was developed to screen people in primary care settings to identify high-risk patients who need further cognitive testing over age of 75 years (62).

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) interventional trial demonstrated that a multimodal lifestyle intervention consisting of dietary guidance, exercise, cognitive training, and control of vascular risk factors helps prevent cognitive decline in older people at increased risk of dementia (63).

In recent years, the coronavirus disease 2019 (COVID-19) pandemic and related measures have also had a negative impact on the lifestyles of older people (64). One of the groups most vulnerable to the pandemic is the population aged 60 and over, who are often living with chronic illnesses and are socially and technically isolated, facing one of the greatest health and economic challenges of recent decades. As a result of isolation, their quality of life (Qol), access to health care, physical and mental health can also deteriorate significantly (65, 66). These factors had a negative impact on the lifestyle of older people in Hungary, too (67).

1.7. Secondary prevention of cognitive decline

Early detection and diagnosis are crucial for most diseases. This can be achieved through targeted screening campaigns, or by professionally carrying out targeted screening tests based on individual risk, suspicion, or indication. Early detection of dementia is a top priority in international dementia prevention strategies (68).

In addition to the Mini-Mental State Examination (MMSE) (69), the clock-drawing test (CDT) (70) and the Mini-COG test (71) are the most widely used. The sensitivity and specificity of these tests vary, with the MMSE not being sensitive enough

to detect mild cognitive deficits (72). The longer, more complex Montreal Cognitive Assessment (MoCA) (73) and Addenbrooke's Cognitive Examination (ACE) (74) are more sensitive neuropsychological tests for measure mild cognitive deficits.

The early detection of mild cognitive deficit, which can be a precursor to dementia, is extremely important (75). Periodic repeated cognitive testing can also detect early-stage mental decline earlier through continuous detection of cognitive decline – 3-5 years follow-up in healthy individuals, 1 year in mild cognitive impairment, and half a year in dementia (76).

Suspected dementia often manifests itself in a variety of behavioural and psychological symptoms rather than cognitive symptoms and is often the underlying cause of acute hospitalizations. Physical examination, quick internal medicine, neurological and laboratory examination of the patient also help to identify possible secondary causes (e.g., hypothyroidism, folic acid and vitamin B12 deficiency) (77).

Magnetic resonance imaging (MRI), positron emission tomography (PET) imaging studies and analysis of cerebrospinal fluid (CSF) biomarkers can help to detect brain lesions more accurately (13). MRI has high sensitivity and specificity in the investigation of dementia; however, it is important to note that a specific protocol must be followed, using appropriate sequences, which include the assessment of cortical areas, hippocampus and the ventricular system, and the use of specific scoring systems (Fazekas, Scheltens, Global Cortical Atrophy, Koedam scale systems) (78). Fluorodeoxyglucose (FDG) PET scans measure reduced glucose metabolism and blood flow in the brain. Amyloid PET or TAU PET scans are used to detect abnormal accumulations of proteins in the central nervous system. Cerebral blood flow single photon emission computed tomography (SPECT) scans can detect regional cerebral perfusion abnormalities, the pattern shows characteristics specific to the type of dementia, and their cost is much lower than PET (79).

Although considerable improvements in neuroimaging methods have made it feasible to comprehend the physiology and structure of the brain in AD, the most direct and practical methods for studying disease progression are biomarker assays based on CSF and plasma. The preclinical and symptomatic stages of AD can be identified using these biomarkers (80). Blood serum amyloid biomarker tests are currently only a method for clinical research, but several large international projects are underway to demonstrate

the clinical diagnostic power of these tests. In addition to amyloid, tau blood tests are also being investigated vigorously (81, 82).

There is a significant body of research on the role of electroencephalogram (EEG) as a biomarker of dementia. The synchronization and the desynchronization of cortical pyramidal neurons and the related functional network organization are investigated by this technique. EEG plays an important role for identifying epileptic discharges in dementia-related epilepsy and can be abnormal in encephalopathies. It also displays some typical patterns in dementia that progresses rapidly (83, 84). A 24-hour EEG scan can also monitor cerebral electrical activity during sleep, it can be a new diagnostic trend in Alzheimer's disease diagnostics. Highly effective spectral, coherence and evoked response analyses are available for detecting MCI, monitoring progression, monitoring drug effects, and differential diagnosis of dementias (85, 86).

Genetic tests are not used to screen for neurocognitive disorders, as gene variants are not a measure of pathological change, but rather an indicator of an individual's risk of developing a pathological change (13, 87). The main diagnostic tools for neurocognitive decline are summarised in **Table 4.**

Table 4. The main diagnostic tools for neurocognitive decline.

Neuropsychological tests
Addenbrooke's Cognitive Examination (ACE)
Clock-drawing test (CDT)
Mini-COG test
Mini-Mental State Examination (MMSE)
Montreal Cognitive Assessment (MoCA)
Medical imaging
Magnetic resonance imaging (MRI)
Positron emission tomography (PET)
Single Photon emission computed tomography (SPECT)
Others
Blood serum biomarker analysis
Cerebrospinal fluid (CSF) analysis
Electroencephalogram (EEG)
Genetic tests

In addition to chronic disease management, the COVID-19 pandemic has had a significant impact on dementia screening worldwide (88-90). In Hungary, the pandemic

and its associated measures have had a negative impact on chronic disease care, presumably including the performance of various screening tests (67).

1.8. Tertiary prevention of cognitive decline

The goals of tertiary dementia prevention activities are the complex care of dementia patients, slowing down the progression of dementia and reducing the chances of further complications. Most people with dementia have multiple co-morbidities, and their care requires a holistic approach and teamwork (91). In a number of cases, in addition to drug therapy, some non-pharmacological interventions, such as music and movement therapy, cognitive training, community activities can also improve the quality of life of people with cognitive decline (92, 93).

Prolonged use of drugs that slow the progression of AD (cholinesterase inhibitors, glutamate regulators) can slow the rate of cognitive decline, delaying the deterioration of patients (94). The treatment of behavioural and psychiatric disorders consists of non-pharmacological and pharmacological interventions, with non-pharmacological interactions recommended as first-line treatment. Symptoms associated with BPSD do not always respond to classical AD medications, so antipsychotics, antidepressants, sedatives, or anxiolytics and antiepileptics are typically prescribed. Guideline-directed antidepressants, antipsychotics and mood stabilizers can help in the treatment of, which are often associated with dementia (95). However, such treatment of BPSD may be complicated by hypersensitivity to antipsychotic drugs (96).

The benefit of low-evidence nootropic agents is not clear and is not mentioned in international guidelines. Since 2021, beta-amyloid anti-monoclonal antibody (aducanumab and lecanemab) therapy for early-stage Alzheimer's disease has been available in the United States (97), with the clinical utility of the product still under debate (98). In patients with early AD, monoclonal antibody therapy with donanemab has also been shown to be effective in improving cognition and the ability to perform activities of daily living, although secondary outcomes have been mixed (99). Medicines that we use to treat the different types of cognitive decline are summarized in **Table 5**.

Table 5. Medicines used in the treatment of cognitive decline. (10, 100)

Therapy to slow the progression of Alzheimer's disease
Donepezil
Rivastigmine
Galantamine
Memantine
Antipsychotics for the treatment of behavioural and psychological symptoms associated with dementia
Tiaprid
Risperidone
Haloperidol
Antidepressants
Selective serotonin reuptake inhibitors (SSRIs)
Nootropic agents
Nicergoline
Piracetam
Vinpocetine
Ginkgo biloba
Anti-beta-amyloid monoclonal antibody
Aducanumab
Lecanemab
Donanemab

Predicting the rate of progression of diseases associated with cognitive decline is important for both patient and family, there are several ongoing studies on this topic. Among these, studies analysing changes in the electrical activity of the brain, which can be detected as epileptic discharges without seizure, play a significant role. Subclinical epileptiform activity (SEA) detected during 24-hour EEG shows promising results in predicting disease progression (101). In line with that, several studies have investigated the therapeutic potential of various antiepileptic drugs (AED) to reduce the risk of cognitive decline and mitigate symptoms associated with BPSD. Of these drugs, the potential role of levetiracetam is the most notable (102-104).

Creating safe living environment for a dementia patient cared for in their home is also extremely important, and in the 21st century, more and more “smart” solutions are being developed to make life safer for dementia patients and more relaxing for family members (105, 106). Tasks related to feeding and fluid intake difficulties, incontinence, pressure ulcers and secondary infections in bedridden patients with severe dementia are also of paramount importance (107) and with appropriate care, a significant proportion of

hospitalizations can be avoided. A high proportion of deaths in people with dementia are caused by bronchopneumonia and ischaemic heart disease (108).

Unfortunately, the COVID-19 pandemic and related measures have also had a negative impact on the lives of people with dementia in their homes, nursing homes and hospitals. (109, 110). In addition, the pandemic and related restrictions have significantly increased the burden on families and caregivers of people with dementia (111, 112).

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2. OBJECTIVES

The objectives of our studies were to investigate the risk factors, comorbid conditions, and progression factors in different spectrums of cognitive decline. Our main goal was to draw attention to the importance of prevention in primary care, both at the very early (Study 1) and late (Study 2) stages of the cognitive continuum.

Our special objectives were:

1. to investigate the impact of the COVID-19 pandemic and the associated restrictions on the lifestyle, quality of life, chronic disease management, physical health and memory impairment of the Hungarian population aged 60 years and over (Study 1);

2. to identify the sociodemographic and comorbid factors, as well as changes in lifestyle and social life associated with the development of subjective cognitive complaints (SCC) and to identify the most relevant predisposing factors for the condition (Study 1);

3. to investigate the prevalence of subclinical epileptiform activity (SEA) detected by 24-hour EEG monitoring in Alzheimer's patients without epileptic seizures and healthy controls (Study 2);

4. to investigate the relevance (impact on cognitive performance and progression of the disease) of subclinical epileptiform activity (SEA) detected by 24-hour EEG monitoring in Alzheimer's patients (Study 2).

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3. METHODS

3.1. Study 1.

3.1.1. Participants

The study was conducted within the framework of the World-Wide (WW)-FINGERS network of multidomain clinical trials for dementia risk reduction (led by Prof. Miia Kivipelto, Karolinska Institute, Sweden) (40). The WW-FINGERS-SARS-CoV-2 initiative was launched in response to the COVID-19 pandemic, under the aegis of the World Health Organization (WHO) Neurology and COVID-19 Global Forum, to assess direct and indirect effects of the pandemic in midlife and older age (64, 113). The survey focused on changes in lifestyle factors, management of chronic noncommunicable diseases, as well as psychosocial factors, all of which are relevant to cognition and are expected to be affected by the pandemic.

Our study was carried out among Hungarian citizens over 60 years of age (67). Inclusion criteria were the followings: 1) age 60+years; 2) living in Hungary; 3) being fluent in Hungarian language; 4) the absence of previous diagnosis of major neurocognitive disorders based on the available medical records. Participation was on a voluntary base and included patients of GP practices and residents of retirement homes. The above categories included healthy elderly participants and patients with various types of chronic diseases. The primary criterion for selection was to find people who could be included in the study cycle, as the data collection period was short and the further progress of pandemic was uncertain, we did not aim for a nationally representative survey, convenience sampling was used.

The survey was conducted between February 1, 2021, and June 1, 2021, with data collected once per participant (time-point analysis). Most of the questionnaires were answered in early spring of 2021, covering the first half of the third wave of the pandemic in Hungary. Methodologically, we used mainly paper-based, self-administered questionnaires; to a lesser extent (5,3%), online surveys and telephone interviews. In total 431 participants answered the Hungarian WW-Fingers SARS CoV2 survey. The vast majority of respondents were patients in GP practices, only a small number of respondents (7%) lived in a nursing home. Data were recorded in the standardized format defined in

the WW-FINGERS consortium, using the OpenClinica web database management application (https://www.openclinica.com/) in an anonymized format. To conduct the study, we applied for ethical approval to the Research Ethics Committee of the National Institute of Clinical Neuroscience, which approved it (reference no.: IKEB 17/2020). All respondents gave written informed consent to participate in the study.

3.1.2. Questionnaire

For the survey, we used the Hungarian translation of the "World-Wide Fingers Sars-Cov-2 Survey". The questionnaire included COVID-19 related questions on health, health care use, lifestyle and activities of daily living, quality of life (QoL), mood and personality, with 46 questions focusing on the following group of questions:

1. Data on sociodemographic and living conditions such as age, sex, level of education, marital status, administrative classification of residence, type of residential building, number and age distribution of people living in a household were collected at the beginning of the questionnaire.

2. In addition to questions on COVID-19 infection (symptomatology, diagnosis, testing, treatment and care, family involvement), we assessed activities related to disease mitigation and transmission reduction measures (vaccination administration, level, and duration of physical and social isolation). Respondents could choose from a range of isolation options and indicate how many weeks they had followed them.

3. The direct and indirect impacts of the pandemic on lifestyle and behaviour (changes in smoking, alcohol consumption, physical activity, social interactions, sleeping, eating, digital device use, media following habits) were also explored in the study. For each item, we asked whether the level was similar, increased or decreased compared to the pre-pandemic situation.

4. In addition to biometric data (weight, height) and changes in these, the questionnaire also analysed non-pandemic diseases (general physical and mental health, chronic diseases) and access to related health care. Participants marked their previously diagnosed chronic conditions on a list; for the conditions marked, we asked if they had experienced any difficulties or changes (cancellation of visits, telemedicine services) in their health care since the begin of the pandemic. Similarly, we measured the availability

of dental care, mental health services, social assistance, and home care services during the pandemic.

5. Additional questions were asked about independent living, the respondent's personality, flexibility, financial situation, mood, quality of life, mobility, volatility, labour market situation. Questions on current and pre-pandemic social life and activity closed the questionnaire, with a seven-point scale for the frequency of participation in each activity, separately for the pre-pandemic and the pandemic period.

3.1.3. Data processing and statistical analysis

IBM Statistical Package of Social Science (SPSS) version 25.0 (https: //www.ibm.com/support/pages/ibm-spss-statistics-25-documentation) and Microsoft Excel were used for statistical analysis. The validity of the data was randomly checked against the questionnaires. The distribution of the data was checked by Kolmogorov-Smirnov test. The results were evaluated using descriptive methods (testing of Objective 1.) (67). Responses were described as a function of distribution for continuous variables using mean and standard deviation or median and interquartile ranges. For categorical variables, data are presented as percentages.

3.1.4. Data extraction and statistical analysis for the prediction of subjective cognitive complaints

For the prediction of subjective cognitive complaints (testing of Objective 2.) (114) we excluded individuals who self-reported prior COVID-19 viral infection confirmed by PCR (n=26) for purpose we did not intend to investigate the direct influence of COVID-19 infection on the subjective cognitive complaints. The presence of minor neurocognitive disorder at the time the data were collected (n=8) and people who did not want to declare their cognitive status (n=4) were further reasons for exclusion. Those participants who reported better subjective memory performance since the beginning of COVID-19 pandemic (n=4) or respondents who cannot judge their memory deterioration compared to the pre-pandemic period (n=30) were also excluded.

After the exclusion, those participants who did not experience any worsening in their memory functions were selected into SCC- group (n=271). Those participants who reported worsening memory functions since the outbreak of the pandemic were selected

into the SCC+ group (n=88). **Figure 2.** displays the flowchart of the participant selection for the SCC prediction.

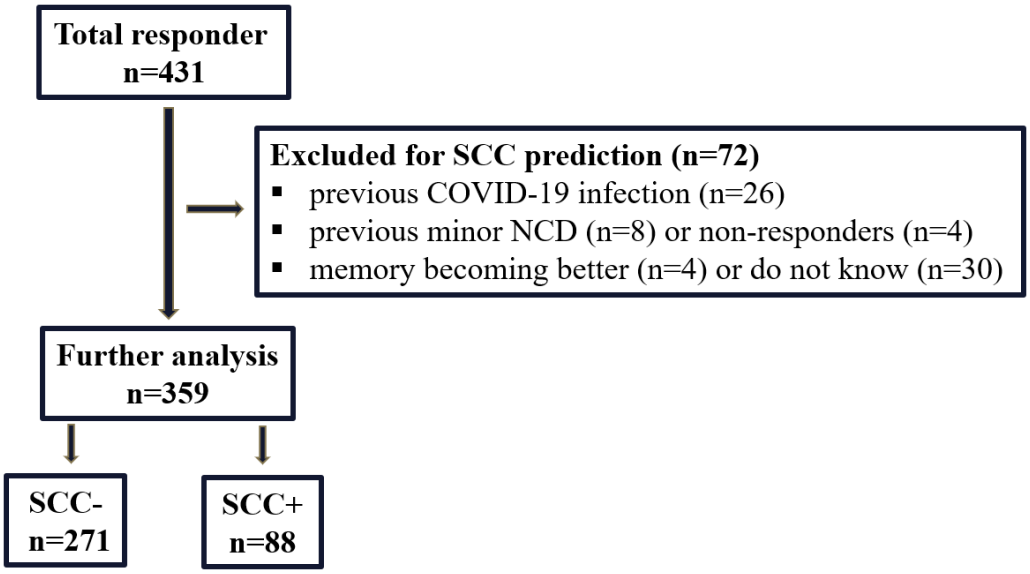

Figure 2. Flowchart of the participant selection for the SCC prediction. (114)
COVID-19: coronavirus disease 2019, NCD: neurocognitive disorders, SCC: subjective cognitive complaints.

From 4 question groups, we chose 5-5 parameters that were in line with the cognitive risk parameters that had previously been reported (34, 43, 57, 63). As a major selection criterion, only statistically independent parameters were included for further analysis. Independence was checked with a correlation matrix where r was set as <0.35 in significant correlations ($p<0.05$) or p was not significant ($p>0.05$). The thresholds are defined based on traditional medical statistical opinions (115).

From the sociodemographic factors age (in years), sex (female, male or prefer not to say categories), educational attainment (in years), family status (possible answers- 1: single, 2: married, 3: living with partner, 4: in relationship, living separately 5: divorced, 6: widowed, 7: prefer not to say) and employment status (possible answers- 1: employed, 2: temporally unemployed due to pandemic, 3: unemployed, 4: pensioner, 5: working as a pensioner, 6: prefer not to say) were selected.

From information regarding pre-pandemic lifestyle, medical conditions and biometric data, pre-pandemic smoking status (scale- 1: no, 2: sometimes 3: daily), pre-

pandemic alcohol consumption (scale- 1: 1-2 international unit (IU), 2: 3-4 IU, 3: 5-6 IU, 4: 7-9 IU, 5: >10 IU/day on days when alcohol was consumed), pre-pandemic body mass index (BMI), current number of chronic disorders and physical independence measured as the capability of independent walking of 500 meters (possible answers- 1: easily able, 2: able but with difficulties, 3: barely able, 4: not able) were selected.

From the lifestyle changes, the followings were selected measured with a 5-point scale (possible answers- 1: significantly decreased, 2: decreased, 3: same, 4: increased, 5: significantly increased): presence of sleep problems, time spent with family, time spent doing physical activity, time spent on remote working, time spent with internet use.

From the social engagement response pool, the followings were selected measured on a 7-point scale (possible answers- 1: daily, 2: few times per week, 3: once per week, 4: few times per month, 5: once per month, 6: less than once per month, 7: never): time for grandchildren, time for voluntary work, time for educational activity, time for sport and social clubs, time for patient organizations. Pre- and post-pandemic responses were compared, and changes were highlighted on a scale ranging from -6 (maximum increase) to +6 (maximum decrease).

Kolmogorov-Smirnov test was used to analyse the distribution of the numerical variables. The appropriate independent samples t-test or Mann-Whitney U-test was used to analyse continuous variables. Chi-squared tests were used to compare categorical variables. All questions' missing response rates were examined, and the difference between the two research groups' missing response rates was compared using Chi-square testing. Responses were viewed as missing variables in cases where individuals preferred not to say. Statistical significance ($p<0.05$) was considered only in variables without significant differences in the distribution of missing responses.

With the 20 variables that were analysed (predictor variables), forward stepwise logistic regression was used to identify possible predictive models for subjective cognitive complaints and to eliminate possible interaction between group differences (116, 117). The response variable was set as the grouping variable (SCC). Predictor variables were continuous variables (age, educational attainment, BMI), categoric variables (sex) or directly generated as categorical variables from scale-based answers.

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Significance of p was set at <0.05. Results of logistic regression were reported with significance levels, odds ratios (ORs) and 95% confidence intervals (CIs).

3.2. Study 2.

3.2.1. Participants

Between 2015 and 2019, the National Institute of Clinical Neurosciences (currently known as National Institute of Mental Health, Neurology and Neurosurgery) in Budapest and the Department of Neurology at the Kaposi Mór County Hospital in Kaposvár, conducted studies on 80 Alzheimer's patients (AD) with clinically typical, primarily memory-associated symptoms who met the diagnostic criteria of the National Institute of Aging-Alzheimer's Association (NIA-AA) (118) for probable AD.

For the purpose of excluding patients who had epileptic seizures or seizure like events, we gathered medical history and medical records. Participants who had epileptic seizures or were at increased risk for epileptic seizures, such as those who had a history of central nervous system infection, clinically significant brain lesions (such as stroke, severe periventricular white matter disease, or white matter infarcts), head injuries that resulted in loss of consciousness, demyelinating conditions, hydrocephalus (n=4), untreated vitamin B12 deficiency (n=5) or hypothyroidism (n=3), syphilis or HIV infection, major depression, schizophrenia or psychoactive drug use (n=9) were excluded. In addition, patients with significant depression symptoms confirmed by neuropsychological testing (n=7) were also excluded.

In total 52 AD individuals' data and 20 cognitively healthy control's (HC) data were examined in the prevalence analysis (year 0 studies). The included patients were divided into subgroups of EEG negative (SEA-), and positive (SEA+) (testing of Objective 3.). Correspondingly, patients with AD were also divided into two groups (AD-SEA vs. AD+SEA) (testing of Objective 4.) (101)**.** All participants in our study were over 60 years old and native Hungarians.

We controlled our AD patients for 3 years and repeated the same battery of neuropsychology test each year. We excluded 5 AD patients from the prospective analysis during the three-year follow-up because they also had serious medical or mental conditions that might have had an impact on cognitive functioning. Four AD patients were excluded from the statistical analysis because they had seizures throughout the follow-up period. Five more patients could not be reached for follow-up. At the end of the 3rd year of the longitudinal analysis we analysed the prospective data of the remaining

38 AD patients (testing of Objective 4.) (101). Based on a landmark study results (119) and our power calculations the probability was equal or greater than 80% to find a significant (alpha=0.05) difference between study groups in MMSE deterioration (in delta MMSE / year) with a sample size of 50. Drop of rate (27%) was higher than calculated. The final number is in line with the expected power calculations.

Figure 3. displays the flowchart of participant recruitment and enrolment in the 3-year follow-up study.

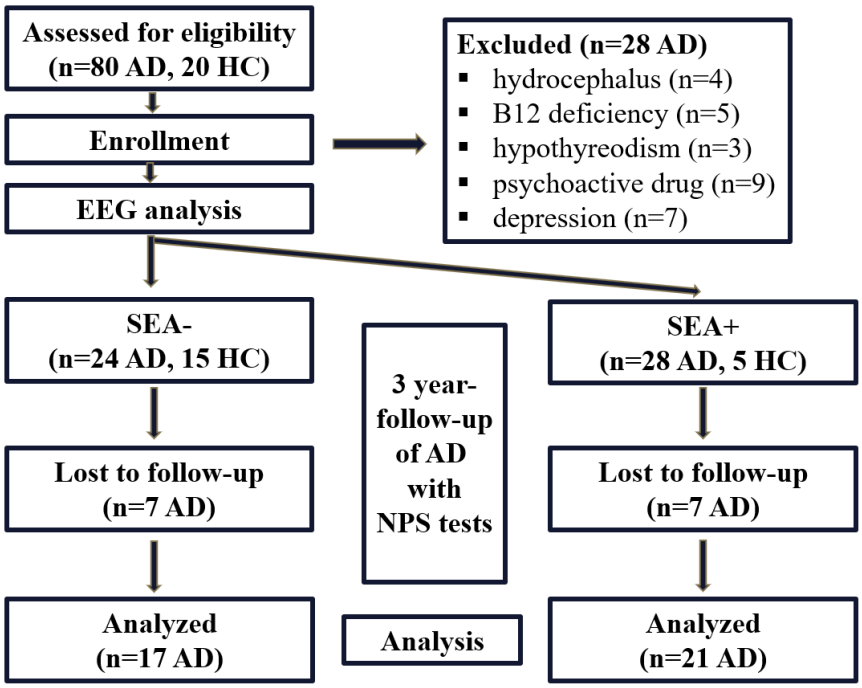

Figure 3. Flowchart of participant recruitment and enrolment in the 3-year follow-up study. (101)

AD: Alzheimer's disease patient, EEG: electroencephalography, HC: healthy control., NPS: neuropsychological, SEA: subclinical epileptiform activity.

To conduct the study, we applied for ethical approval to the Hungarian Medical Research Council, which approved it (reference no.: 024505/2015/OTIG). All participants gave written informed consent to participate in the study. Since all of the AD cases were mild enough that every patient could consent on their own behalf, surrogate consents were not necessary.

3.2.2. Clinical testing, neuropsychological examination

The participants went thorough physical, neurological, and epileptological testing, as well as routine blood tests to examine their levels of vitamin B12 and thyroid function. Magnetic resonance imaging (MRI) of the structural brain was done on each individual.

Neuropsychological tests were administered by qualified neurologists or neuropsychologists. This was done a total of 4 times during the follow-up study: at the beginning of the study (year 0), and at the beginning of each succeeding year (year 1, year 2, and year 3), within 335–395 days after the last examination. We used the Hungarian version of Addenbrooke Cognitive Examination (ACE) (120, 121) as primary test battery because of its high sensitivity and specificity in the diagnosis of major neurocognitive disorders (122). ACE scores range from 0 to 100. ACE measures six cognitive domains including orientation, attention, memory, verbal fluency, language, and visuospatial skills. It serves properly in the assessment of dementia severity since Mini-Mental State Examination (MMSE) Score can be extracted from the test data (123). The ratio of verbal fluency and language skills divided by the scores of orientation and delayed recall memory (VLOM ratio) helps to distinguish frontotemporal dementia and AD. VLOM ratio typically range from 2.2 to 3.2. Initially, value below 2.2 indicated frontotemporal-type deficiency and values above 3.2 indicated Alzheimer-type impairment (124).

The participants have also taken the Hungarian versions of the Beck Depression Inventory II (BDI-II) (125) and the Spielberger State and Trait Anxiety Inventory (STAI)(126). To increase our diagnostic accuracy, patients with a STAI> 45 and a BDI II >13 were not included in our analysis.

The controls had no cognitive complaints, they had normal brain MRI and blood results, normal neurology status, and normal neuropsychology scores, MMSE score >26 (127), ACE score >84 (120), STAI <45 (126), BDI II <13 (125).

3.2.3. EEG examination

We performed 34-channel 24-hour long EEG recording (Micromed Morpheus, 10-20 electrode placement system) in all participants within 5 days following the neuropsychological and clinical testing at the beginning of the study (year 0). During the follow-up period EEGs were not repeated. The following EEG settings were used: bipolar

longitudinal montage, 10 microvolts/mm sensitivity, 30 mm/sec speed, 70 Hz low pass and 0.5 Hz high pass filter with 50 Hz notch filter on.

Subclinical epileptiform activity (SEA) was defined as paroxysmal EEG graphoelements (spikes or sharp waves) with 20-200 ms duration, with the disruption of background EEG activity, followed by slow waves (128). The EEGs were visually rated by two separate raters; a graphoelement was marked as epileptiform activity if both raters indicated it as such. The diagnoses were hidden from both raters. We identified and excluded from the calculation the following variations in order to prevent incorrect interpretation of epileptic transients: wicket spikes, occipital sharp transients of sleep, benign epileptiform transients in sleep, and rhythmic temporal theta series in superficial sleep. The patients were divided into subgroups of EEG negative (SEA-), and positive (SEA+) persons based on these evaluations.

The number of spikes was visually counted. The average number of spikes/hours was calculated as the total number of spikes divided by the hours of recordings. The temporal distribution of SEAs was analysed according to sleep stages.

The scalp distribution of SEA was analysed both visually and with the application of automatic EEG software (Micromed SystemPLUS 98, Compumedics NeuroScan Curry 7). Recognition of spatial distribution of SEA was based on the largest electronegativity corresponding to scalp electrodes in the 10-20 electrode placement system as follows: frontal (Fp1, Fp2, F3, F4), frontocentral (Fz), central (C3, Cz, C4), centroparietal (Pz), frontotemporal (F7, F8), temporal (T3, T4, T5, T6), parietal (P3, P4) and occipital (O1, O2) electrodes.

3.2.4. Data processing and statistical analysis

IBM SPSS version 20.0 (https://www.ibm.com/support/pages/ibm-spss-statistics-20-documentation) and Microsoft Excel were applied for statistical analysis.

Shapiro-Wilk test was used to assess the distribution. For pairwise comparisons, Mann-Whitney U-test was used for data with a non-parametric distribution, and t-tests were employed for continuous data with a parametric distribution. Chi-square test was used for pairwise categorical variable comparisons. Holm-Bonferroni correction method was used to adjust for multiple comparisons. Since AD patients constituted an older

group, logistic regression was used to compare the prevalence of SEA between AD patients and healthy controls (HC).

Repeated measure general linear model (GLM) was used to assess longitudinal changes in the neuropsychological data represented by the ACE score and MMSE score between AD+SEA and AD-SEA patients (at the beginning, after 1-year, after 2-year, and after 3-year follow up). Shapiro-Wilk test results showing a normal distribution of the ACE and MMSE data ($p>0.05$) led to the selection of the linear model. Between subject factor was the presence (AD+SEA) or absence of epileptiform activity (AD-SEA), while the measured ACE and MMSE scores at 0 time point, at 1-year, at 2-year and at 3-year represented the within subject variable (dependent factor). Given that sphericity could not be assumed ($p<0.05$) according to Mauchly's test results, the Greenhouse-Geisser adjustment was used to present the p- and F-values for pairwise comparisons. To examine changes over time, Tukey-test was used for post-hoc analysis with Bonferroni correction. We report adjusted p-values for the multiple comparisons of 4 time points (0-, 1-, 2-, 3-year) and indicate significance where $p<0.0125$. Several known progression-modifying variables were included in the model as covariates, including gender, education level (expressed as years of education), and disease severity (expressed as 0 timepoint MMSE score). These components' effects as determined by the linear model were reported. $P<0.05$ indicated an impact that was statistically significant.

The progression of cognitive impairment and spike frequency were correlated using Spearman's correlation. The spatial distribution of spikes and the progression of cognitive decline were compared by ANOVA analysis.

The data produced from the long-term EEG recording carried out at year 0 were used for all statistical analyses including EEG data.

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4. RESULTS

4.1. Study 1.

4.1.1. Demographics and clinical characteristics

The majority of questionnaires (83%) were completed in February and March 2021. A total of 431 people took part in our study, almost two thirds of them were women. The vast majority of respondents were patients in GP practices, a small number of respondents, only 7% (30/431) lived in a nursing home. Their average age is around 74 years and the vast majority have at least a secondary school education. Almost a third of respondents live alone, and 81% of them live in the capital or in a city with a population of more than 40,000. Sixty-seven percent of respondents live in an apartment, 26% in a detached or semi-detached house and 7% in a nursing home. By the time the questionnaire was completed, 6% of respondents were confirmed by PCR to be infected with COVID-19. The demographic data are summarized in **Table 6.**

Table 6. Demographic data of participants. (67)

COVID-19: coronavirus disease 2019, SD: standard deviation.

Parameter			
Number of total participants in the survey (n)			431
	Mean (years)	**SD**	**Correct completers (n)**
Age	73,54	8,19	406
Education	14,45	4,15	417
	Participant (n)	**%**	**Correct completers (n)**
Female sex	270	62,64	431
Living alone	138	32,85	420
Living in the capital or big city	347	81,45	426
Confirmed COVID-19 infection	26	6,03	431
Patient with chronic disease	369	85,61	431

4.1.2. Impact of the pandemic on lifestyle

The increase in using of the internet and digital devices is obvious in the population studied. In terms of diet, although snacking has increased, fruit and vegetable consumption has not changed significantly. However, the extent of this is not known, so

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it is possible that it was not at a satisfactory level before the period under review, and if it has not increased, it could be considered a negative effect. This cannot be inferred from the present study. Smoking and alcohol consumption did not increase according to the self-report questionnaire and appetite was not particularly affected by the pandemic. There was no change in family disagreement or fear of violence. However, nearly half of the respondents felt themselves less physically active, their sleep had deteriorated, their future felt more hopeless, and they felt lonelier. Pandemic had the most negative impact on spending time with family and friends, with nearly 80% of respondents experiencing a decrease. **Figure 4.** displays the impact of the pandemic on the changes of lifestyle factors.

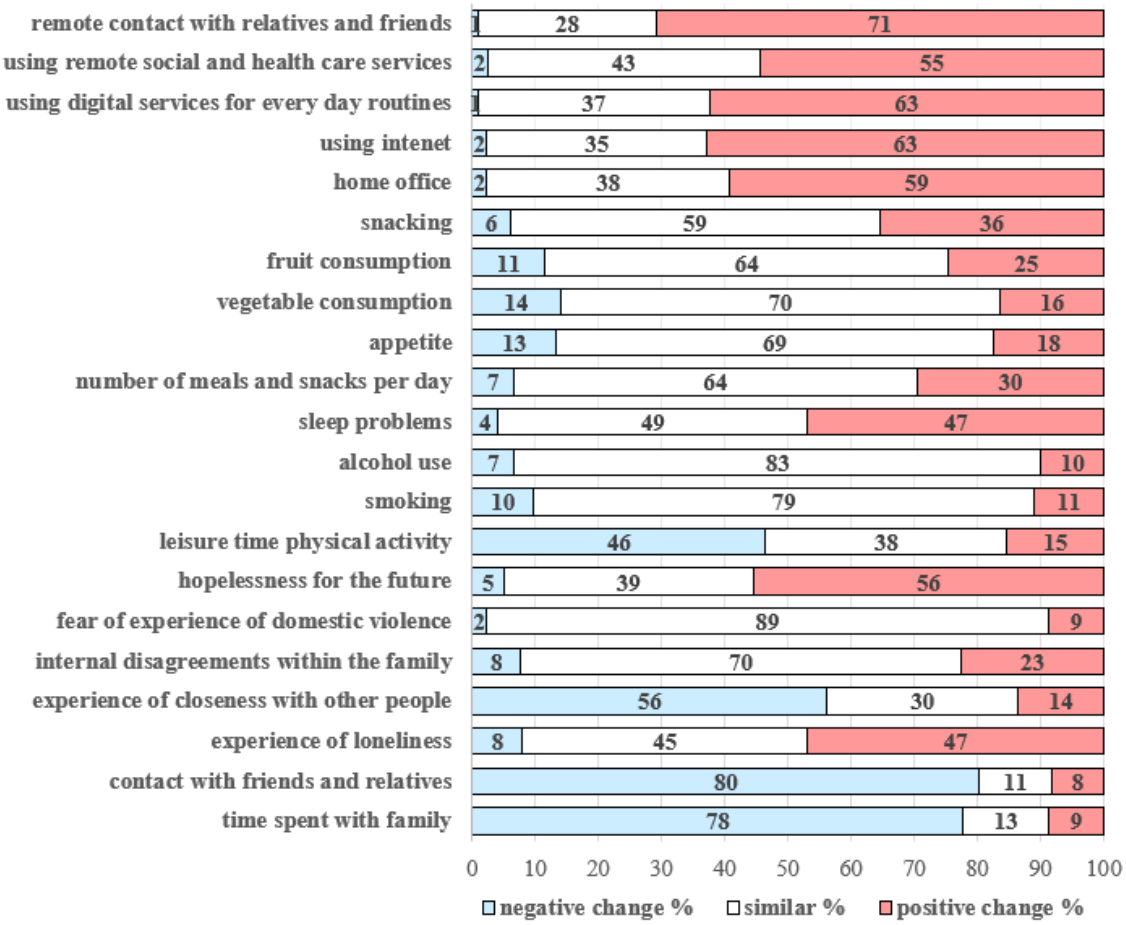

Figure 4. Changes in lifestyle factors during third wave of the COVID-19 pandemic in the Hungarian population aged 60 years and over. (67)

The figure reflects the percentage distribution of respondents.

4.1.3. Impact of the pandemic on the care of acute patients, chronic patients, and social care

Total 86% of respondents (n=369) indicated at least one chronic disease, for a total of 877, i.e., an average of more than two chronic diseases was diagnosed in these patients. Among these, hypertension was the most common (76%), while a higher proportion had been previously diagnosed with elevated cholesterol (43%), cardiovascular disease (28%), diabetes (22%), musculoskeletal disorders (16%), psychiatric disorders (14%), cancer (7%), and asthma and COPD (7-7%). By their own admission, only 15% of chronic patients requested a doctor-patient encounter for the conditions they were followed for. The vast majority received the medical care they thought they needed: the visit was a face-to-face appointment in 56% of cases, and a telephone or online visit in 21% of cases. In just less than a quarter of cases, the visit was cancelled; in 14% of cases the patient cancelled the visit and only in 9% of the visits were cancelled by the healthcare provider.

Around a quarter of respondents (110 people) required dental treatment during the pandemic, which was provided in 65% of cases. Similar proportions were seen for emergency care, mental health services, consultations with a social worker, and home care for the elderly or disabled; but here there was a total need for only 34 visits, of which 22 were provided.

4.1.4. Impact of the pandemic on the health in general, quality of life, and subjective memory

The health status of most respondents did not change during the pandemic, only 20% of respondents rating their health as worse than before the pandemic. However, the deterioration in quality of life is more relevant, with 45% of respondents rating their current quality of life as worse than before the pandemic outbreak. Twenty-five percent of the total respondents felt their memory was worse than before. It is worth mentioning, however, that 54% of the 26 participants, who previously had COVID-19 infection confirmed by PCR, felt their memory worse than before the pandemic. The exact distribution of responses is illustrated in **Figure 5.**

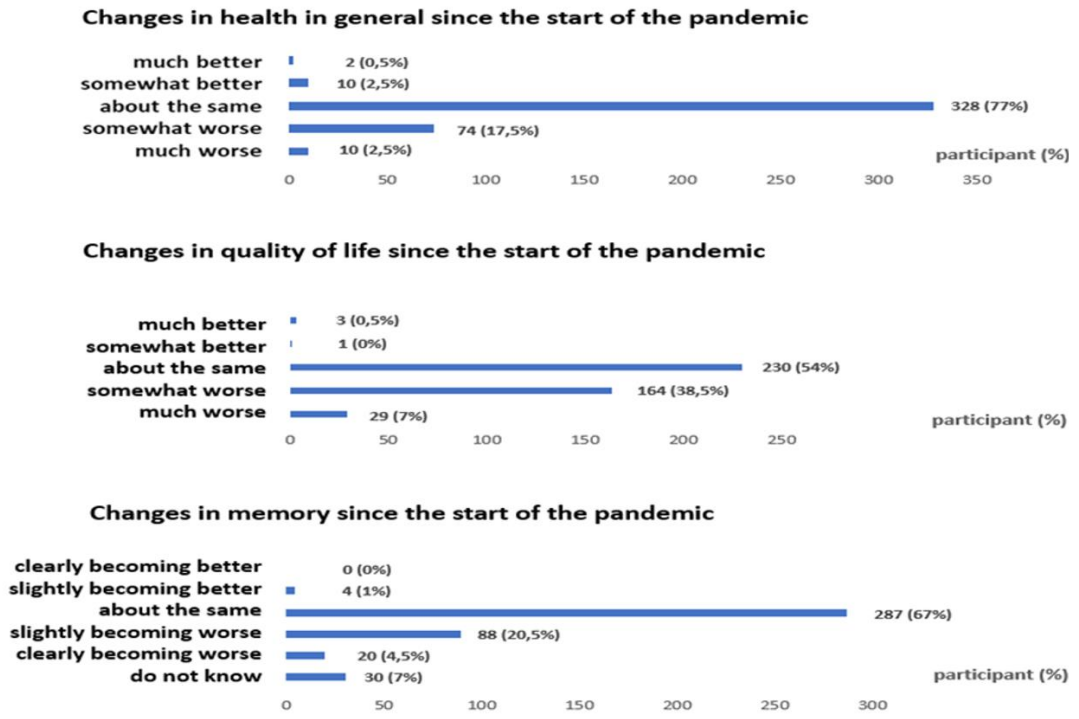

Figure 5. Subjective changes in general health, quality of life and memory in the study sample. (67)

The figure shows the number of respondents within each response category.

4.1.5. Predisposition to subjective cognitive complaints

After exclusion, the responses of 359 participants (age: 73.6±7.9, 223 females) were evaluated for the statistical analysis of SCC prediction.

Those 75,5% of participants (n=271) who had intact cognitive performance before the pandemic and did not experience any change in their memory functions were included in the non-SCC (SCC-) group. The remaining 24,5% (n=88) who had normal cognitive performance preceding the pandemic but reported worsening memory performance since the outbreak of the pandemic were selected into the SCC (SCC+) group. Fifty-one % of SCC+ group (n=45) expressed concern regarding their memory worsening.

4.1.5.1. Sociodemographic factors

The SCC+ cohort had a higher percentage of women (Chi-score=21.1; $p<0.001$) and was significantly older than the SCC- cohort (MD=3.6 years; $p<0.001$). The missing response rate did not differ statistically between the two parameters listed above. The

SCC+ cohort had more educational years on average than the SCC- group, but the difference was not statistically significant. The most prevalent marital status was "married" in both study groups, however there were more married participants in the SCC- group (54.2%) than in the SCC+ group (44.6%). Parallel to this, the SCC+ group had a disproportionate number of divorced (10.8% vs. 7.2%) and widowed (30.1% vs. 25.4%) people. While 15% of subjects in the SCC- group and 19% in the SCC+ group were working after retirement, the most prevalent work status in the population was pensioner (72.1 % in the SCC- and 72.6 % in the SCC+ groups). Only 8% of the participants in the survey were in active employment. The statistical results of between group comparisons are presented in **Table 5.**

4.1.5.2. Pre-pandemic physical condition

While the SCC+ population had a greater percentage of daily smokers (12.6% vs. 8.9%), the majority of individuals (88.6% in the SCC- group and 85.1% in the SCC+ group) did not smoke. Most of the respondents (80.4% in the SCC- group and 86.21% in the SCC+ group) were light drinkers who consumed 1-2 international units per day on the days when alcohol was consumed. The SCC- group had a higher prevalence of moderate alcohol use (3–4 IU/day) (16.9% vs. 6.9%), while the consumption of more than 4 units of alcohol per day was more prevalent in the SCC+ group (6.9% vs. 2.7%). Mild obesity was seen in both groups, with an average BMI of 26.6 in the SCC- group and 27.4 in the SCC+ group. There was a high prevalence of chronic illnesses reported; only 16.7% of SCC- and 6.9% of SCC+ patients reported no chronic conditions. At least two chronic diseases were present in 58% of SCC- patients, while the prevalence was even higher in the SCC+ group (76.4%). According to these findings, the measured population was characterized by polymorbid chronic medical illnesses; however, the SCC+ group had a significantly larger number of comorbid diseases ($U=8354.5$; $p<0.001$). This may be supported by physical mobility measurements, as fewer patients in the SCC+ group (58.6%) than in the SCC- group (86.9%) reported being able to walk 500 meters without any problems. Only 3% of SCC- individuals and 10.3% of SCC+ participants, respectively, were unable to walk on their own. The reported difference was significant. The missing response rate was not statistically different in physical independence and the

number of chronic illness categories. The statistical results of between group comparisons are presented in **Table 5.**

4.1.5.3. Changes in lifestyle

In the SCC+ group, sleep problems were more common than in the SCC- group (70.5% vs. 33.1%). Less than 3% of the respondents reported an improvement in subjective sleep quality. Both groups significantly reduced the amount of time spent with family; 78% of participants, regardless of which group they were in, reported a major reduction, while only 7% reported an increase in this activity. The frequency of physical activity reduced in a considerable number of individuals as well (20% of the SCC+ group and 11.5% of the SCC- group showed a significant reduction, while 32.9% of the SCC+ group and 29.5% of the SCC- patients showed a mild reduction). Only 13% reported at least slightly increased sport activities without significant intergroup differences. Fifty-three percent of SCC- individuals and 77% of SCC+ subjects reported more remote work. Reduction was indicated in less than 1% of the participants. While compared to SCC- participants, SCC+ patients showed a higher decline in physical activity as well as an increase in sleep problems and remote working. Seventy-six percent of SCC+ patients vs. 55.9% of the SCC- patients reported more intensive internet use with statistical significance (p's<0.001). The only parameter with no significant differences in missed answer rates is internet use. The statistical results of between group comparisons are presented in **Table 5.**

4.1.5.4. Changes in social engagement

A third of respondents (35.1%) reported spending less time with grandchildren. In the SCC+ group, consistency was reported less frequently (54.6% vs. 62.7%). The most frequent change in both groups (15.9% in the SCC+ population and 12.6% in the SCC- group) was a 1-point decline; however, the SCC+ population as commonly had a significant 4-point decrease (10.23% in SCC+ vs. 3.3% in SCC- group). Only minimal changes in volunteer work (11%) and educational activities (10%) were noted. Since 17% of respondents reported less time spent in sport and social clubs (a 3.2-point drop in the average), there was a small decrease in that time. Only 10.5% of respondents said they spent less time in patient organizations; however, the shift was small (1.1 points on

average). Between the study groups, there were significant missing response variations in every category. The statistical results of between group comparisons are presented in **Table 7.**

Table 7. Characteristics in the different cognitive risk parameters of SCC- and SCC+ participants. (114)

SCC: subjective cognitive complaints.

As data demonstrates, there was a large variety among the missing responses between the two study groups. Intergroup differences were considered relevant only in the cases where groups did not differ significantly in the missing response rate ($p>0.05$).

Bold signalling indicates the statistically significant differences between the study populations with the consideration of the above-mentioned circumstances.

[a] Defined in mean±SD. Statistically compared with t-test, where * indicates significant p (<0.05).

[b] Defined in %. Statistically compared with Chi-square test, where * indicates significant p (<0.05).

[c] Defined in median (interquartile range). Statistically compared with Mann-Whitney U-test, where * indicates significant p (<0.05).

[d] Possible answers- 1: single, 2: married, 3: living with partner, 4: in relationship, living separately 5: divorced, 6: widowed, 7:

[e] Possible answers- 1: employed, 2: temporally unemployed due to pandemic, 3: unemployed, 4: pensioner, 5: working as a pensioner, 6: prefer not to say

[f] Possible answers- 1: no, 2: occasionally 3: daily

[g] Possible answers- 1: 1-2 international unit (IU), 2: 3-4 IU, 3: 5-6 IU, 4: 7-9 IU, 5: >10 IU/day)

[h] Possible answers for ability to walk 500m independently- 1: easily able, 2: able but with difficulties, 3: barely able, 4: not able

[i] Possible answers- 1: significantly decreased, 2: decreased, 3: same, 4: increased, 5: significantly increased

[j] Possible answers- 1: daily, 2: few times per week, 3: once per week, 4: few times per month, 5: once per month, 6: less than once per month, 7: never. Pre- and post-pandemic

responses are highlighted on a scale ranging from -6 (maximum increase) to +6 (maximum decrease)

Effect size is measured in Cohen's d in the variable category, where 0.2-0.5=small effect, 0.5-0.8=medium effect, >0.8=large effect.

As the Table indicates, in the differences in physical independence, even large effect sizes are observed, while in the rest of the parameters, small effect sizes are presented.

Key: SCC subjective cognitive complaints, BMI body mass index.

Parameter	**SCC-**	**Prefer not to say (%)[b]**	**SCC+**	**Prefer not to say (%)[b]**	**p-value (effect size in Cohen's d)**
Number of participants	271	-	88	-	-
Sociodemographic factors					
[a]Age (years)	**72.6±7.4**	0%	**76.2±8.9**	0%	1 **<0.001* (0.44)**
[b]Sex (% of females)	**61%**	0%	**65%**	0%	0 **<0.001* (0.24)**
[c]Educational attainment (years)	14.5 (12-17)	2.5%	15.0 (12-17)	4.5%	<0.001* (0.61) 0.66 (0.15)
[b,d]Family status		1.8%		4.5%	<0.001* (0.83)
-single (%)	7.95%		8.43%		0.631 (0.12)
-married (%)	54.17%		44.58%		<0.001* (0.24)
-living with partner (%)	3.41%		6.02%		<0.001* (0.63)
-in relationship, living separately (%)	1.89%		0%		<0.001* (0.61)
-divorced (%)	7.2%		10.84%		<0.001* (0.42)
-widowed (%)	25.38%		30.12%		<0.001* (0.18)
[b,e]Work status		0.7%		4.5%	<0.001* (1.90)
-employed (%)	7.43%		7.14%		<0.001* (0.09)
-temporally unemployed due to pandemic (%)	0.37%		1.19%		<0.001* (0.14)
-unemployed (%)	0.74%		1.19%		<0.001* (0.42)
-pensioner (%)	72.12%		72.62%		<0.001* (0.13)
-working as pensioner (%)	18.59%		15.48%		<0.001* (0.11)
-invalid (%)	0.37%		2.38%		<0.001* (1.40)
Prepandemic physical condition and lifestyle					
[b,f]Prepandemic smoking		0%		1.1%	<0.001* (0.69)
-no (%)	88.56%		85.06%		<0.001* (0.03)
-occasionally (%)	2.58%		2.3%		<0.001* (0.09)
-daily (%)	8.86%		12.64%		<0.001* (0.31)
[b,g]Prepandemic alcohol consumption (international unit/day)		16.2%		34%	<0.001* (0.55)

-1-2 (%)	80.43%		86.21%		<0.001* (0.22)
-3-4 (%)	16.85%		6.9%		<0.001* (0.76)
-5-6 (%)	1.63%		5.17%		<0.001* (0.95)
-7-9 (%)	1.09%		0%		<0.001* (0.45)
- >10 (%)	0%		1.72%		<0.001* (1.12)
[c]Prepandemic BMI (kg/m^2)	26.6 (24-29.7)	2.9%	27.4 (24-30.6)	1.1%	<0.001* (0.86) 0.35 (0.12)
[c]Prepandemic number of chronic diseases (number)	**2 (1-3)**	0.59%	**2 (1-4)**	0.55%	0.67 (0.11) **<0.001* (0.46)**
[b,h]Physical mobility (walking 500m independently)		1.15%		1.1%	0.29 (0.06)
-easily able (%)	**86.89%**		**58.62%**		**<0.001* (0.36)**
-able with difficulties (%)	**7.12%**		**26.44%**		**<0.001* (0.89)**
-barely able (%)	**3%**		**4.6%**		**<0.001* (0.37)**
-not able (%)	**3%**		**10.34%**		**<0.001* (0.87)**
Changes in lifestyle during the pandemic					
[b,i]High quality sleep time		38.7%		30.6%	<0.001* (0.11)
-decreased (%)	33.13%		70.49%		<0.001* (0.72)
-same (%)	63.86%		27.87%		0.207 (0.88)
-increased (%)	3.01%		1.64%		0.04* (0.63)
[b,i]Time for family		12.9%		12.5%	<0.001* (0.13)
-decreased (%)	79.06%		77.92%		<0.001* (0.20)
-same (%)	13.68%		15.58%		<0.001* (0.11)
-increased (%)	7.26%		6.49%		<0.001* (0.15)
[b,i]Time for physical activity		19.9%		20.4%	<0.001* (0.03)
-decreased (%)	41.01%		52.86%		<0.001* (0.21)
-same (%)	42.86%		35.71%		0.003* (0.23)
-increased (%)	16.13%		11.43%		0.039* (0.18)
[b,i]Time for remote work		78.5%		85.2%	<0.001* (0.07)
-decreased (%)	1.72%		0%		0.192 (0.67)
-same (%)	44.83%		23.08%		0.094 (0.62)
-increased (%)	53.45%		76.92%		<0.001* (0.39)
[b,i]Time for internet use		24.7%		24.6%	0.91 (0.03)
-decreased (%)	**1.96%**		**0%**		**0.001* (0.47)**
-same (%)	**42.16%**		**24.7%**		**<0.001* (0.42)**
-increased (%)	**55.88%**		**75.93%**		**<0.001* (0.32)**
Changes in social engagement during the pandemic					
[b,j]Time for grandchildren		9.1%		10.1%	<0.001* (0.19)
-decreased (%)	33.58%		42.05%		<0.001* (0.24)
-same (%)	62.73%		54.55%		<0.001* (0.18)
-increased (%)	3.69%		3.41%		<0.001* (0.17)
[b,j]Time for voluntary work		10.3%		10.9%	<0.001* (0.16)
-decreased (%)	6.27%		9.09%		<0.001* (0.34)
-same (%)	91.51%		88.64%		<0.001* (0.21)

-increased (%)	2.21%		2.27%		<0.001* (0.07)
[b,j]Time for educational activity		7.6%		6.6%	<0.001* (0.15)
-decreased (%)	8.49%		7.95%		<0.001* (0.19)
-same (%)	90.41%		88.64%		<0.001 (0.11)
-increased (%)	1.11%		3.41%		<0.001* (0.78)
[b,j]Time for sport and social clubs		13.4%		11.9%	<0.001* (0.21)
-decreased (%)	20.3%		12.5%		<0.001* (0.33)
-same (%)	78.23%		86.36%		<0.001* (0.11)
-increased (%)	1.48%		1.14%		<0.001* (0.15)
[b,j]Time for patient organizations		16.3%		12.8%	<0.001* (0.29)
-decreased (%)	9.59%		13.64%		<0.001* (0.27)
-same (%)	89.67%		84.09%		<0.001* (0.12)
-increased (%)	0.74%		2.27%		<0.001* (0.79)

4.1.5.5. Factors associated with subjective cognitive complaints

The factors connected to SCC were examined using forward stepwise logistic regression. The applied model demonstrated that only two parameters, physical mobility, and independence (ability to walk 500 meters without difficulty; OR=1.186; p<0.001; 95%CI=1.101, 1.270) and changes in time spent with grandchildren (OR=1.04; p=0.015; 95%CI= 1.008, 1.073) determined the outcome of the respondents. The reported model, which just took into account physical mobility, had an R-square of 0.082, while the model that took into account both factors had an R-square of 0.108. Between the two models, there was a significant improvement in R square values (p=0.026). **Figure 6.** demonstrates the differences in physical mobility and in negative changes of time spend by grandchildren of SCC- and SCC+ participants.

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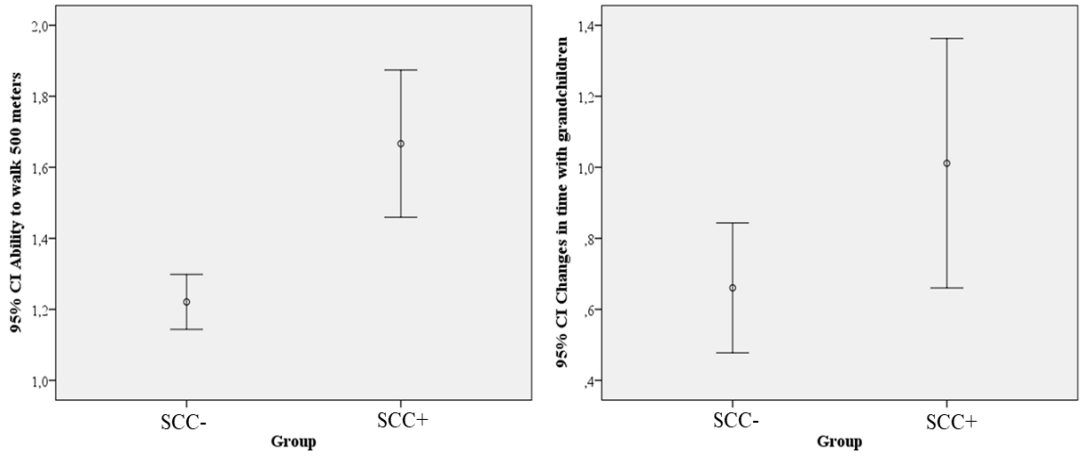

Figure 6. Differences in physical mobility and in negative changes of time spent with grandchildren between SCC- and SCC+ participants. (114)

SCC: subjective cognitive complaints

Logistic regression revealed that the key parameter indicating the development of SCC is the reduced physical mobility. Physical mobility was assessed on a 4-point scale where higher scale indicates poor performance. The second important contributor of SCC in our sample is the time spent with grandchildren, responses were compared on a 7-point scale assessing the estimated time before and during the pandemic, positive change indicates less time with grandchildren.

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4.2. Study 2.

4.2.1. Demographics and clinical characteristics at year 0

In comparison to the control group (n=20), the AD group (n=52) was significant older (75.5±8 vs. 67.8±4.8 years, p=0,01), therefore statistical analysis needed a correction for age. We found SEA in 54% (28/52 patients) of AD patients (AD+SEA) and in 25% (5/20 patients) of HCs, the difference was statistically significant (p=0.018).

All AD patients were in the mild or moderate phase of dementia, neuropsychology revealed that they had typical AD-related cognitive impairment (deficit predominantly in orientation and episodic memory). When MRIs were visually analysed, all cases showed hippocampal atrophy typical of AD as well as bifrontal-bitemporal atrophy. **Table 8.** summarized demographics and clinical parameters of participants.

Table 8. Demographics and clinical parameters of participants. (101)

ACE: Addenbrooke Cognitive Examination, AD: Alzheimer's disease, MMSE: Mini-Mental Score Examination, SD: standard deviation, SEA: subclinical epileptiform activity, VLOM ratio: sum of verbal fluency and language scores divided by sum of orientation and delayed memory recall scores. Statistical tests were Chi-square for sex, SEA and handedness; t-test for age; Mann-Whitney U-test for number of years of education, MMSE score, ACE score and VLOM ratio.

*Bold signalling indicates significant differences (p<0.05).

Parameter	**Controls**	**AD patients**	**p-value**
Number of patients	20	52	-
SEA+ (n, %)	**5 (25%)**	**28 (53,8%)**	***0.018**
Female sex (n, %)	9 (45%)	31 (59,6%)	0.346
Age (years, mean±SD)	**67.8±4.8**	**75.5±8**	***0.01**
Right handedness (n, %)	18 (90%)	48 (92.3%)	0.772
Number of years of education median score (interquartile range)	12 (12-17)	12 (12-17)	0.142
MMSE median score (interquartile range)	**28.5 (27.3-29)**	**20 (16-23)**	***<0.001**
ACE median score (interquartile range)	**92.5 (89.3-94.8)**	**66 (56-74)**	***<0.001**
VLOM median ratio (interquartile range)	**2.7 (2.5-3)**	**3.4 (3.2-4.1)**	***<0.001**

4.2.2. Spatial and temporal distribution of subclinical epileptiform activity in Alzheimer's patients at year 0

SEA was primarily present over the temporal electrodes (23/28 patients; 82%). Left temporal SEA (12/23 patients; 52%) lateralized more frequently than right temporal (5/23 patients; 22%) or bitemporal (6/23 patients; 26%) occurrences. **Figure 7. Panel A, B, C** displays the spatial distribution of SEA.

Spike frequency ranged from 0.29 to 6.68 per hour in SEA patients (on average 2.02 per hour).

The majority of spikes (92%) occurred during sleep. While 23% of spikes were found in stage 1 sleep, stages 2 (31%) and 3 (34%) sleep saw the highest rates of spike appearance. Only 4% of spikes occurred during rapid eye movement (REM) sleep. **Figure 7. Panel D** displays the temporal distribution of SEA.

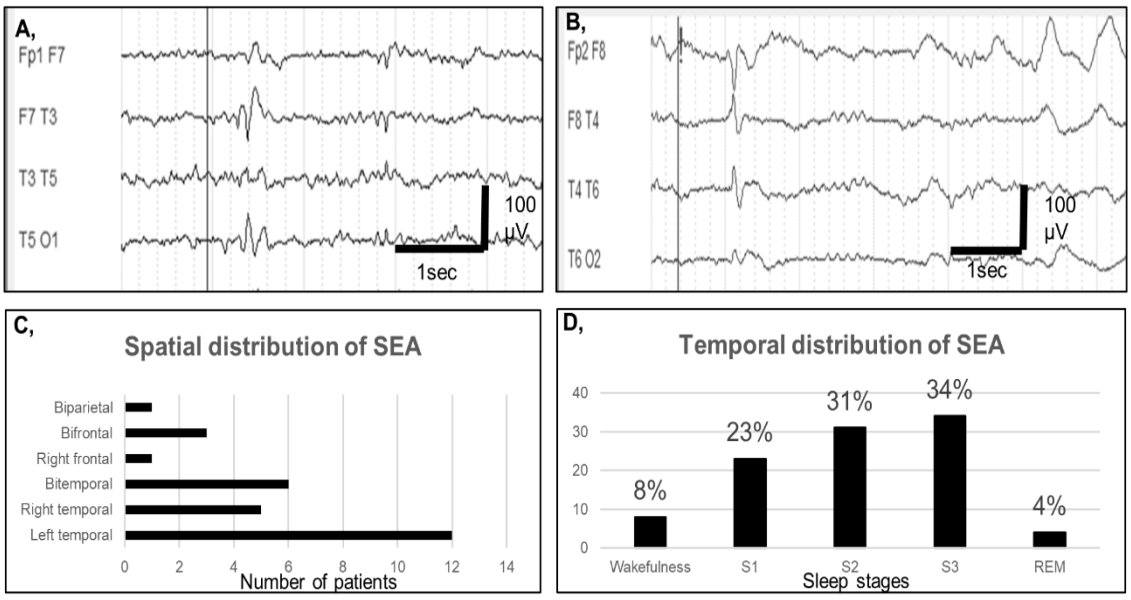

Figure 7. Neurophysiologic features of subclinical epileptiform activity (SEA) in AD patients at year 0. (101)

Panel A: Spike detected in the left temporal region with phase inversion at temporal (T3) electrode in patient 005; **Panel B**: Spike detected in the right frontotemporal region with maximum electronegativity at frontal (F8) electrode in patient 008; **Panel C**: Spatial distribution of SEA showing the dominant occurrence of spikes in the temporal regions

with left sided predisposition.; **Panel D**: Temporal distribution of SEA demonstrating that spikes occur almost exclusively in sleep, dominantly in deep sleep.
S1, S2, S3: stage 1, 2, 3 sleep, REM: rapid eye movement

4.2.3. Characteristics of Alzheimer's patients with and without subclinical epileptiform activity at year 0

We separated our AD patients into two subgroups based on the presence or absence of SEA in the EEG recordings: AD+SEA (n=28) and AD-SEA (n=24) respectively. The presence of SEA did not significantly change the clinical or epidemiologic characteristics of AD patients. They did not display any variations in treatment approach, handedness, dementia progression, or overall neuropsychology scores. Additionally, those who were in the AD+SEA subgroup, had increased (but not statistically significant) VLOM ratios. **Table 9.** demonstrates the epidemiologic and clinical data of the AD+SEA and AD-SEA subgroups.

Table 9. Epidemiologic and clinical data of AD+SEA and AD-SEA patient groups. (101)
ACE: Addenbrooke Cognitive Examination, AD: Alzheimer's disease, MMSE: Mini-Mental Score Examination, SEA: subclinical epileptiform activity, VLOM ratio: sum of verbal fluency and language scores divided by sum of orientation and delayed memory recall scores, SD: standard deviation.
Statistical tests were Chi-square for sex, antidementia medication and handedness; t-test for age and onset of disease; Mann-Whitney U-test for number of years of education, MMSE score, ACE score and VLOM ratio.

Parameter	**AD-SEA**	**AD+SEA**	**p-value**
Number of patients	24	28	-
Female sex (n, %)	14 (58%)	17 (61%)	0.579
Memantine therapy (n, %)	5 (20%)	6 (21%)	0.51
Cholinesterase inhibitor therapy (n, %)	24 (100%)	28 (100%)	1
Age (years, mean±SD)	73.5±7.8	71.9±7.5	0.441
Right handedness (%)	21 (88%)	27 (96%)	0.321
Age at the onset of dementia (years, mean±SD)	70.7±7.5	69±7.4	0.434

Duration of dementia in years with median (interquartile range)	3 (1-4)	3 (2-3)	0.76
Number of years of education median (interquartile range)	12 (12-12)	12 (12-17)	0.26
MMSE median score (interquartile range)	19.5 (16-24.8)	20 (16-21.8)	0.665
ACE median score (interquartile range)	66 (58.5-69)	65 (55.3-77)	0.919
VLOM median ratio (interquartile range)	3.4 (3.2-3.6)	3.6 (3.3-4.6)	0.07

According to the analysis of several ACE subscores related to different cognitive domains in the AD patients, AD+SEA had lower performance in memory (Md=3.84; p=0.007) and visuospatial scores (Md=1.05; p=0.03). After Holm-Bonferroni correction, the difference in memory remained significant (p<0.008). **Table 10.** demonstrates the cognitive domain specific characteristics of AD-SEA and AD+SEA patients.

Table 10. Domain specific characteristics of Addenbrooke's Cognitive Examination subscores of AD-SEA and AD+SEA patient groups at year 0. (101)

AD: Alzheimer's disease, SEA: subclinical epileptiform activity.

Mann-Whitney U-test was applied for pairwise comparisons.

* Bold signalling indicates significant differences (p<0.008, after Holm-Bonferroni correction).

Parameter	**AD-SEA**	**AD+SEA**	**p-value**
Number of patients	24	28	-
Orientation median score (interquartile range)	7 (5.25-7)	7 (6-8)	0.061
Attention median score (interquartile range)	6 (4-7)	6 (5-8)	0.308
Memory median score (interquartile range)	**22.5 (19.25-27.75)**	**19.5 (17-21)**	***0.007**
Verbal fluency median score (interquartile range)	8 (7.25-9)	8.5 (5.5-11)	0.445
Language median score (interquartile range)	19 (16-20)	20 (18-22.5)	0.16
Visio-spatial median score (interquartile range)	4 (3-4)	3 (1-3)	0.03

Figure 8. shows the differences in memory median score and visio-spatial median score between the two AD subgroups.

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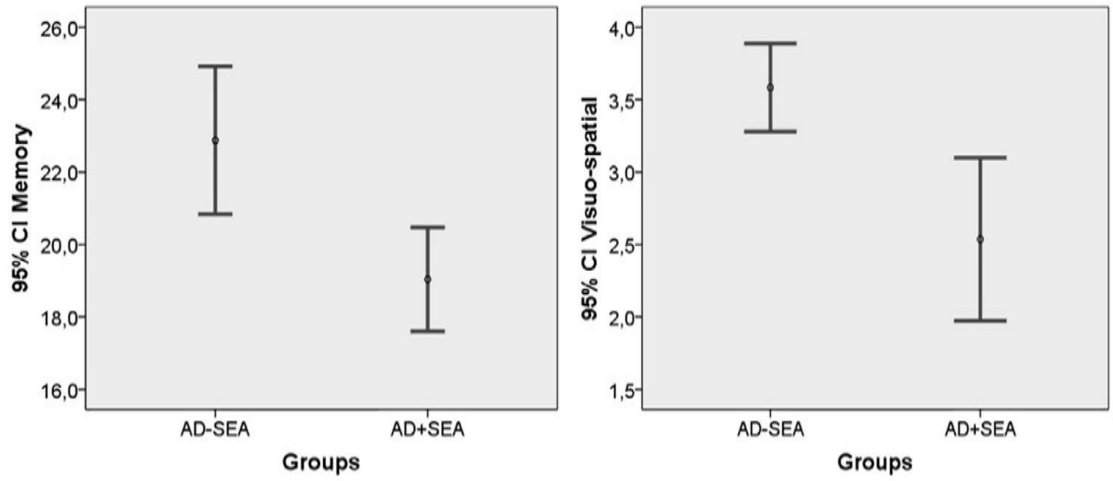

Figure 8. Differences in memory median score and visio-spatial median score of AD-SEA and AD+SEA patient groups at year 0. (101)

4.2.4. Prospective analysis of the effect of subclinical epileptiform activity on the progression of Alzheimer's disease at year 3

In our prospective study we analysed the data of 38 AD patients who completed the 3-year follow-up. Only the VLOM ratios between AD+SEA patients (n=21) and AD-SEA patients (n=17) were significant different (Md=-0.57; p=0.039). **Table 11.** summarize the baseline epidemiologic and clinical data of the AD-SEA and AD+SEA patient groups that completed the 3-year prospective follow-up.

Table 11. Baseline epidemiologic and clinical data of AD-SEA and AD+SEA patient groups that completed the 3-year prospective follow-up. (101)

ACE: Addenbrooke Cognitive Examination, AD: Alzheimer's disease, MMSE: Mini-Mental Score Examination, SD: standard deviation, SEA: subclinical epileptiform activity, VLOM ratio: sum of verbal fluency and language scores divided by sum of orientation and delayed memory recall scores.

Statistical tests were Chi-square for sex, antidementia medication and handedness; t-test for age, onset of disease, for ACE score; Mann-Whitney U-test for number of years of education, MMSE score and VLOM ratio.

* Bold signalling indicates significant differences ($p<0.05$).

Parameter	AD-SEA	AD+SEA	p-value
Number of patients	17	21	-
Female sex (n; %)	11 (65%)	11 (52%)	0.33
Memantine therapy (n; %)	4 (24%)	5 (24%)	0.94
Cholinesterase inhibitor therapy (n; %)	17 (100%)	21 (100%)	1
Age (years, mean±SD)	74.2±7.3	71.5±5.9	0.22
Right handedness (n, %)	17 (100%)	21 (100%)	1
Age at the onset of dementia (years, mean±SD)	70.8±7.2	68.6±5.5	0.304
Duration of dementia in years with median score (median; interquartile range)	3 (3-4)	3 (3-3)	0.055
Number of years of education in median score (interquartile range)	12 (12-14.5)	12 (12-17)	0.857
MMSE median score (interquartile range)	18 (15.5-22.5)	20 (16-21)	0.37
ACE score (mean±SD)	65.5±9.1	65.5±12.5	0.98
VLOM median ratio (interquartile range)	**3.3 (3.2-3.5)**	**3.6 (3.3-4.5)**	***0.039**

In the follow-up AD+SEA group, the spatial distribution of SEA at year 0 was as follows: 33% (7/21 patients) left temporal, 24% (5/21 patients) right temporal, 19% (4/21 patients) bitemporal, 5% (1/21 patients) right frontal, 14% (3/21 patients) bifrontal, and 5% (1/21 patients) biparietal.

In the longitudinal analysis, AD+SEA patients showed significantly faster cognitive decline as demonstrated by average yearly decreases in total ACE scores (12.15 points per year in AD+SEA patients versus 8.17 points per year in AD-SEA patients, $F=15.891$; $p<0.001$) and average yearly decrease in MMSE scores (2.71 points per year in AD+SEA patients versus 2.22 points per year in AD-SEA patients, $F=9.64$; $p=0.01$). Cohen's d effect size was 1.53 for 3-year ACE decline and 0.86 for 3-year MMSE decline. Significant differences were found with Tukey post-hoc analysis across all the measured time points (1st, 2nd, and 3rd years) in ACE and MMSE scores (all p's<0.001). The covariance weighted analysis using the beginning of dementia (years), sex (% of females), educational level (total years), and disease severity (MMSE score) at the 0 timepoint continued to show that the 1.5 times greater decrease in ACE and 20% greater decrease in MMSE in the presence of SEA were significant. Only the MMSE score at the 0 timepoint shown a significant progression-modifying effect in our sample ($F=9.661$;

p<0.001 for ACE; F=8.212, p=0.01 for MMSE). **Figure 9.** shows that AD+SEA patients had 1,5-times higher cognitive decline in total ACE scores than AD-SEA patients.

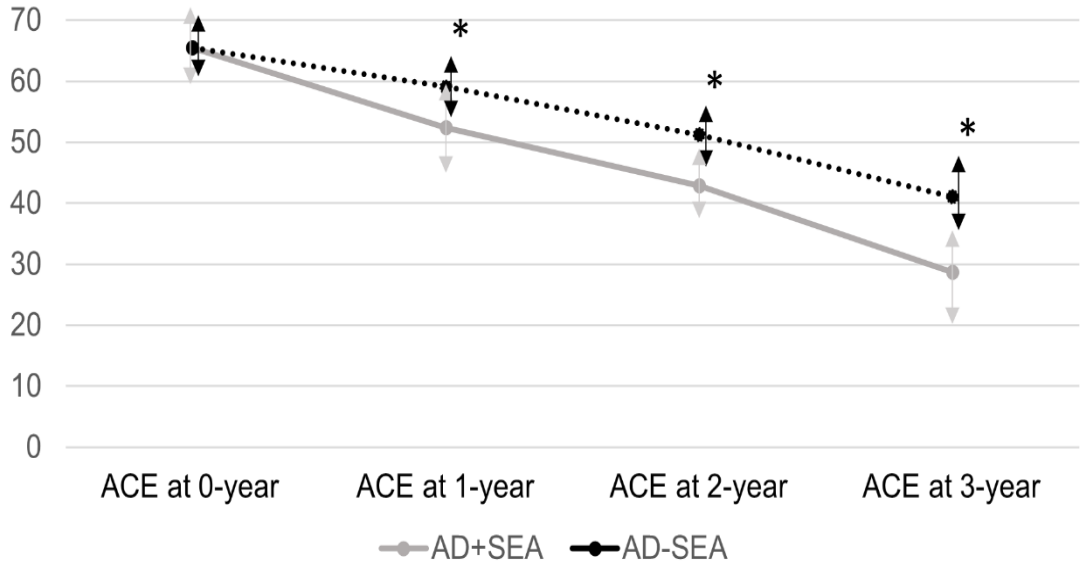

Figure 9. Results of longitudinal prospective follow-up at year-3 in relation to decline in total Addenbrooke's Cognitive Test score in AD+SEA and AD-SEA patient groups. (101)

ACE: Addenbrooke's Cognitive Examination, AD: Alzheimer's disease, SEA: subclinical epileptiform activity.

AD+SEA patients show significant (p<0.001), 1.5-times higher decline in total ACE scores than AD-SEA patients using repeated general linear model. * Indicates significant differences (p<0.001).

The decline in ACE score had a statistically significant positive correlation (r: +0.664; p<0.001) with the measured baseline spike frequency (year 0). **Figure 10. Panel A** shows the correlation between cognitive decline in ACE scores and spike frequency. We additionally identified a minor but significant correlation (r: +0.48; p<0.01) between spike frequency and MMSE score reduction.

Since we found higher prevalence of spikes in the temporal regions with prominent left sided occurrence, we also measured the potential effect of spatial distribution of spikes on the progression of cognitive decline with ANOVA analysis

comparing left, right and bitemporal appearances (n=16). We found non-significant trend for differences (F:3.775; p=0.051) across the 3 groups, where left did not differ from bitemporal occurrence (p=1), while right occurrence was associated with lower non-significant decrease in ACE than left appearance (Md=11.85; p=0.058). **Figure 10. Panel B** illustrates the relationship between the baseline spatial distribution of spikes and the degree of cognitive decline in the follow up.

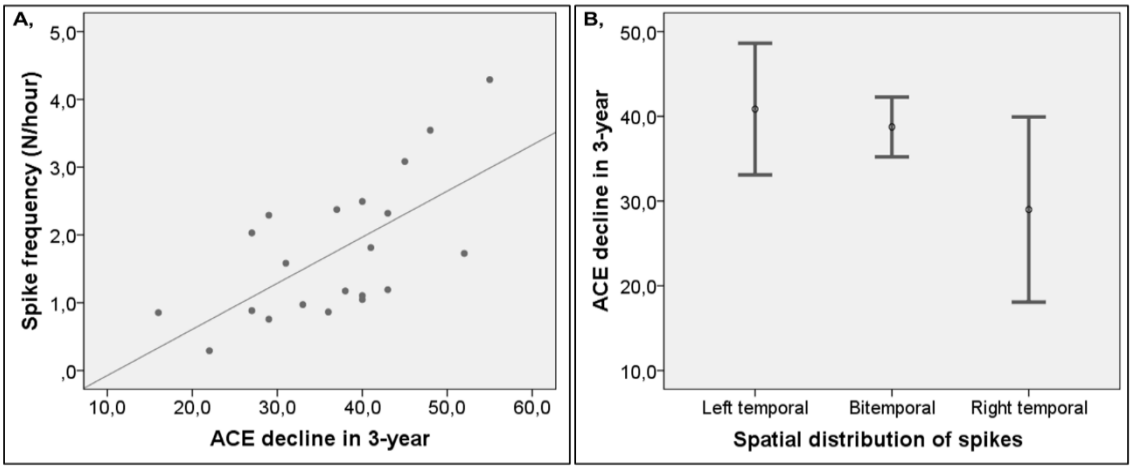

Figure 10. Results of longitudinal prospective follow-up at year-3 in relation to baseline (year-0) frequency and spatial distribution of epileptiform spikes. (101)

Panel A: Decline in ACE scores shows strong positive (r:+0.664) and significant (p<0.001) correlation with spike frequency. **Panel B**: Left temporal (n=7) and bitemporal (n=4) spikes associate with faster cognitive decline than right spikes (n=5) with marginal significance (p:0.051).

ACE: Addenbrooke's Cognitive Examination.

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5. DISCUSSION

5.1. Study 1.

Our first study presents the results of the "World-Wide Fingers Sars-Cov-2 Survey" in Hungary. In recent years, the COVID-19 pandemic has had a significant impact on the lives of humanity as a whole, especially the elderly as one of the most vulnerable population groups (129, 130). In addition, in the technologically accelerated world, the ageing population faces many new types of challenges that have a significant impact on lifestyle, mental and physical health, and cognitive performance. Some of these may be potentially modifiable risk factors for cognitive decline. Investigating the role of these factors in predisposing to SCC may help to reduce the burden of dementia.

We surveyed 431 elderly people, mostly from the capital and its agglomeration areas, with higher-than-average educational backgrounds, 7% of all participants was resident in nursing homes. The number of participants exceeded the expectations of the WW-FINGERS Consortium, allowing for European regional comparisons. Local results in some countries are already available (64, 131, 132). Due to the length and complexity of the survey, a large number of people with higher education participated in completing it, the sample was non-representative, convenience sampling was used.

The sample had a low rate of confirmed COVID-19 infection (6%), suggesting that the results of our analysis primarily reflect the importance of the containment measures surrounding the pandemic rather than the impact of the infection. The study period coincided with the third wave of the COVID-19 pandemic in Hungary, at the beginning of the vaccination activity, when the rate of decline in relative mortality among older people may be the result of rapidly increasing vaccination coverage (133). Unfortunately, there are no precise data on the infection rate among the elderly in that period of the pandemic in Hungary. A representative cross-sectional survey of the Hungarian population conducted after the first wave of COVID-19 showed that the overall infection rate was relatively low, in line with the previous SARS-CoV-2 exposure prevalence (134).

The proportion of people with chronic illness in the sample was significant, affecting almost 90% of respondents. The majority of participants were diagnosed with

two illnesses. The distribution of chronic diseases in our sample is good representation for this age group in Hungary, with none of the disease groups was over-represented (135).

5.1.1. Impact of the pandemic on the lifestyle, healthcare, mental and physical health of elderly

Regarding lifestyle factors, based on the epidemiological recommendation for the population, our results show a prominent increase in the use of digital services, while time spent with family and close friends has decreased dramatically. Lifestyle habits have changed in a negative direction, with a deterioration in the quality of the diet, more frequent sleep problems and lower level of physical activity. There has been an increase in digital services among respondents (71%), in line with changes seen in other countries (136, 137) and this is clearly a consequence of limited social contacts and frequent work at home (138). This could undoubtedly benefit from an acceleration in the growth trend of digitalisation of healthcare and virtual telemedicine visits, which could reduce the workload of the healthcare system (139, 140). This is supported by the fact that 55% of respondents in our survey reported that they use digital services more often for remote social and health purposes.

Only 15% of the respondents felt that a medical consultation with a specialist was needed due to their chronic illness. This rate can be also explained by the low level of health awareness among the Hungarian population and the low availability of various preventive opportunities in Hungary (141). Almost a third of the visits that took place were online rather than traditional. While this can help to reduce the burden on healthcare system and open new patient pathways, that can also create the basis for social inequalities. Our sample represents people living in or around the capital with a relatively high level of education. It is known that the potential for telemedicine use is low among those living in rural areas or with lower education levels, or among those belonging to minorities and lower income groups (142). In the case of many diseases, continuous follow-up is an essential tool at different levels of prevention (143). About a quarter of medical visits for chronic conditions were cancelled, in most cases this was at the request of the patients, which may have been due to fear of the infection (144). In nearly two-thirds of cases, the necessary dental treatments were provided, facilitated by a

professional protocol or guideline (145). Due to the low number of cases no conclusions can be drawn on the care of acute illnesses and social care. Because of the negative lifestyle changes and reduced access to specialist examinations and checkups, COVID-19 pandemic has had a detrimental effect on various levels of prevention, presumably also for dementia (146, 147).

It is important to note the decline in subjective perceptions of general health status was not highly represented in our sample, but a decrease in subjective quality of life (QoL) was found in nearly half of the respondents, which could have important consequences. This observation is in line with other data that have also reported worsening subjective well-being and health-related QoL as a result of pandemic-related restrictions (148, 149). This may be particularly important in light of the fact that reduced subjective well-being is associated with a significant increase in the prevalence of mood disorders and cardiovascular disease (150) and a significant decrease in survival expectancy (151).

In our survey about a quarter of respondents experienced subjective cognitive complaints since the beginning of the pandemic, more than half of them are concerned about this. Several studies have shown that lockdown had a detrimental effect on memory performance in older people (152-155). The increased prevalence of SCD and decreased subjective well-being are presumably a mutually reinforcing, bidirectional relationship (156).

An important observation was that more than half (n=14) of the 26 participants who had confirmed COVID-19 infection reported subjective cognitive complaints, while a quarter of the respondents without previous COVID-19 infection reported SCC. Due to the low rate of COVID-19 infection in our sample, we cannot draw any major conclusions, but several studies investigating post-COVID symptoms report higher rates of subjective memory complaints in COVID-19 infected individuals (157, 158).

5.1.2. Factors predisposing to the development of subjective cognitive complaints

It is noteworthy that, even though we have not screened for dementia, our cohort represented an SCD plus category (34) because: 1) the participants predominantly reported memory impairment; 2) symptoms developed in the past 5 years; 3) respondents were over 60 years of age. The analysed population gives particular significance to our

results considering studies showing that SCD plus individuals have the highest risk of developing MCI or later dementia (34).

Data analysis was complex as the two groups measured clearly showed significant differences in terms of missing responses. However, participants with SCC displayed unique traits in comparison to people without SCC: 1) they were older, 2) they were more likely to be women, 3) they had more chronic diseases on average, 4) they showed more prominent impairment in physical mobility, and 5) they used the internet more frequently during the pandemic (all p's<0.001).

As regards the analysis of sociodemographic factors, our results show that the number of people suffering from subjective cognitive complaints increases with age. Not surprisingly, several studies have also shown an age-related increase in the prevalence of dementia and MCI (159-161). The currently available literature also supports the notion that women are more likely than men to experience cognitive problems. Recent research indicates that women have a higher chance of developing AD (162) are more likely to exhibit cognitive symptoms in the presence of AD, even in the preclinical stage (163, 164), and have a higher conversation rate from MCI to AD (165). Our analysis found no correlation between the development of SCC and educational level, marital status, or employment status; however, because of the unique design of our data collection and the stark differences between study groups, it is challenging to extrapolate these findings to missing responses. As lower levels of education are associated with a higher risk of dementia (166), one possible explanation for our results is the high education of the entire studied population. According to several studies, living alone raises the risk of SCD (167) and dementia (168). We distinguished a variety of marital status categories, which could reduce the discriminative effect compared to other studies utilizing just stringent grouping factors (living with partner or without), which were used in other studies. However, in our sample also showed a higher percentage of divorced and widowed status in the SCC+ group. Although it is known that older age at retirement is associated with a reduced risk of dementia (169); shift work and long-term night work are modestly associated with a higher risk of developing dementia (170). Since the inclusion criterion for our sample was age over 60 and the average age of participants was 74 years, the impact of work status is hardly detectable.

Nearly 90% of the responders had a chronic disease, with the majority of them have been diagnosed with two different diseases. A higher number of co-existing chronic diseases were found in the SCC+ group. Numerous studies have verified the function of co-morbidity in the development of SCC (171-173). It is well known that in most cases, as the number of chronic diseases rises, so do the patient's immobility and vulnerability. However, the traditional cardiovascular risk factors should be avoided to prevent dementia (63). Reduced physical activity and immobility are currently regarded as a significant risk factor of cognitive deterioration (43, 174, 175). Our findings further underlined the crucial and leading predictive significance of reduced physical activity and immobility in the development of SCC. Participants were in both group on average in the slightly overweight category based on their BMI. Given that both populations reported only having a modest dose of alcohol use (mild drinkers) and a relatively low frequency of smoking, it is likely impossible to measure the impact of alcohol and smoking, which also play a significant role as risk factors for cognitive decline (176, 177).

Among the changes in lifestyle factors, the increase in internet use should be highlighted in our study. Over 60% of respondents reported an increase in internet use and daily use of digital devices. Although the regular internet use is associated with approximately half the risk of dementia than non-regular usage (178), increased internet use can reduce time spent on physical activity, which can lead to anxiety (179) and increase feelings of loneliness (180). Our data suggest that increased use of digital services has not led to increased social contact, even though this could have enabled by more frequent use of these services. Another important consideration is that increased digital living space for older people can reduce feelings of isolation (181) , but increased use leads to a drastic reduction in satisfaction in this population based on large samples (182). Previous research has shown that increased internet use is often associated with reduced sleep time, later bedtimes and earlier wake-ups (183). This factor is also significant in our study, with sleep disturbances becoming more pronounced in nearly half of respondents, which has been associated with a decline in subjective memory in several studies (184-186). Interestingly, because of the large number of missing responses for this group of questions, the impact of the other factors cannot be assessed.

Investigating of social engagement is important, as it is known that those who have been more socially active are less likely to experience cognitive decline, and social

engagement can help reduce the risk of further cognitive decline (187). In terms of changes related to social engagement, the most notable was a decrease in time spent with grandchildren. The role of family and social contacts in the prevention and the progression of cognitive decline has long been investigated (188, 189). Presumably, the other examined activities studied were not significantly presented in the sample before the pandemic, so their changes cannot be interpreted.

The results of the stepwise logistic regression showed that the most significant factors related to SCC were the physical immobility and a decrease in time spent with grandchildren. These findings highlight the importance of physical activity and close social relationships as a key aspect of healthy brain ageing that is usually overlooked, although many studies have demonstrated their importance (43, 190-192).

5.1.3. Limitations

Our research has some important limiting factors. Due to the specificity of the international questionnaire, a self-completion cross-sectional test was used, health data on the previous physical and mental health status of the participants were only partially known, and their assessments were based on the subjective opinion of the respondents. Our results may have been influenced by the fact that some respondents were unaware of their COVID-19 infection or denied it. Changes in life situation could not be controlled for and were also self-reported changes. It can be assumed that these changes were mostly caused by the pandemic and the associated restrictions. The data collection follows a specific design, which makes it difficult to generalize these characteristics. No memory screening test was performed. Our sample reflects a specific, highly educated, well-cooperating population. Due to the uncertainty around the epidemic, our survey was not representative, convenience sampling was used. Our results are based mainly on data from people living in or outside the Hungarian capital and are therefore not generalizable. The large variation in missing responses complicates comparisons on a number of parameters. This fact also highlights a common problem in dementia research analysing the impact of sociodemographic factors.

5.1.4. Clinical relevance and future directions

To our knowledge, this study is the first in our area that examined the risk factors for subjective memory disorder in a larger sample size. The strengths of our study were the relatively large number of elderly people who completed our complex questionnaire and the uniform structure of the survey. These allow international comparisons to be made among the countries participated in the survey. Further of the strengths of the survey was not conducted with a specific group of patients, none of the patient groups were over-represented. Our study highlighted the indirect effects of COVID-19 pandemic. This had a negative impact on the lifestyle, mental and physical health of a significant proportion of the elderly population. Our study draws attention to the importance of early prevention, in particular of modifiable risk factors for cognitive decline, in which primary care has a significant role. Our results suggest that particular attention should be paid to older, polymorbid, physically immobile, socially isolated populations at increased risk of cognitive decline. To reduce cognitive decline in older people, it is important to highlight the importance of maintaining physical mobility, in which regular physical activity plays a significant role. The role of close family and social relationships can also be an important protective factor against the development of cognitive decline. It is particularly important to raise awareness in society of these factors of early prevention, health policy makers can play an important role in this. Additional joint analyses and further longitudinal studies are required to determine the potential risk factors.

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5.2. Study 2.

In our second study, we investigated the role of cortical hyperexcitability detected by 24-h EEG in Alzheimer's patients with no history of epileptic seizure. It is well known that epilepsy and Alzheimer's disease are common neurological disorders for which increasing age is a well-known risk factor (193-195). Based on the results of human and animal studies, epileptic activity can often be associated with Alzheimer's disease (196-198). Seizures in patients with Alzheimer's disease are often unrecognizable, as they usually take the form of non-motor seizures and may overlap with other symptoms of the disease, even with BPSD. The presence of SEA may affect the manifestation of BPSD (199). In patients with AD, seizures can accelerate cognitive decline, highlighting the clinical importance of early recognition and treatment of epileptiform discharges (200-202).

We investigated 52 Alzheimer’s patients and 20 healthy controls in our study. Based on another study results (119) and our power calculations our sample size was large enough. All Alzheimer's patients included in the study had mild to moderate dementia. This can be explained by the need for patient cooperation to participate in the study and the follow-up nature of our study. Even for follow-up studies aimed at preventing dementia, there are many challenges (203, 204).

5.2.1. Epileptiform discharges in healthy and Alzheimer's patients

Recent research has revealed that cortical hyperexcitability has a role in the pathophysiology of AD (205, 206). Subclinical epileptiform activity (SEA) can be a reliable neurophysiological indicator of cortical hyperexcitability (207, 208).

In our study we found that the prevalence of SEA is much higher in AD patients than in control individuals (54% vs. 25%). The relatively high prevalence of SEA in both population is surprising, but previous studies have also reported that older adults who are not epileptic have a higher risk of epileptiform events (205, 209, 210). In a study using ear-EEG, epileptiform discharges were detected in 75% of Alzheimer's disease patients and 46.7% of HC patients. Long-term ear-EEG monitoring detects epileptiform discharges in most AD patients, with a threefold increased spike frequency compared to HC, probably originating from the temporal lobes (211). Our notably high SEA rate may

be explained by the fact that we looked at 24 hours of EEG data, which included an entire night of sleep. Which is relevant because the study of AD-related sleep changes is important as a potential target for improving sleep and slowing cognitive decline (212).

Numerous epilepsy studies have demonstrated that interictal epileptiform discharges accumulate during sleep (213, 214). A previous study demonstrated that 1-hour sleep recordings are much more sensitive than 1-hour awake EEGs in detecting epileptiform activity (215). Therefore, the enhanced sensitivity of long-term EEG incorporating sleep recordings is a potential reason for our discovery of a raised SEA rate. Another study on the temporal distribution of SEA in AD found that 90% of all epileptic activity occurred during sleep and 42% of AD patients had SEA, which is consistent with our observations (119). The relationship between sleep and memory has long been studied (216). It is now accepted that sleep disorders are an integral part of neurodegenerative diseases and it is known that the treatment of sleep disorders in the context of neurodegenerative diseases should be individualised (217). Sleep has an active role in information processing, with non-rapid eye movement (NREM) being predominantly responsible for processing declarative content and rapid eye movement (REM) sleep for processing non-declarative content (218, 219). During NREM sleep, acquired information is reactivated and integrated into long-term memory, which is stabilized by a synaptic consolidation process during REM sleep (220).

The frontotemporal dominance of the epileptiform activity is not unexpected given the known temporal and frontal involvement of AD-related morphological changes (221, 222). The overwhelming left dominance of epileptiform activity is surprising, because this neurodegenerative disease is thought to be symmetric or at least bilateral (223). However, consistent with our results, other studies analysing interictal epileptiform discharges found a similar spatial distribution (205, 224, 225).

The significantly different methodologies of other studies make it difficult to compare spike frequencies, which vary widely, as in our study (119, 226, 227).

5.2.2. Effect of baseline epileptiform discharges on memory performance

In our study the presence of SEA did not correlate with lower global cognitive scores at diagnosis. However, further analysis showed that the presence of SEA was associated with more severe memory and visuospatial subscore impairment in ACE. The

diagnostic role of the different cognitive domains was examined in a number of studies. Impaired visuospatial abilities may potentially play a role in assessing the progression of cognitive decline (228-230).

Several studies investigated the therapeutic potential of antiepileptic drugs (AED) in Alzheimer's disease (231, 232). Results from a randomized clinical trial of levetiracetam showed that although the treatment did not significantly alter cognitive function, it was estimated to improve executive function and spatial memory in 60% of cases in participants with Alzheimer's disease identified by extended neurophysiological imaging as having seizures or SEA (104). The successful use of AED in reducing the symptoms of BPSD raises the possibility of SEAs in the background of fluctuating BPSD. Future research should investigate whether cortical excitability is relevant to therapeutic approaches to the cognitive and neuropsychiatric symptoms of Alzheimer's disease (233, 234). In next-generation clinical trials, quantitative neurophysiological measurements can be used to improve diagnosis and select the right patients for appropriate therapy, as they are sensitive biomarkers of network hypersensitivity (235). Our results raise the possibility that SEA may also serve as a marker of faster disease progression in the later stages of Alzheimer's disease.

5.2.3. Effect of baseline epileptiform discharges on cognitive decline progression

To better understand and predict the Alzheimer’s disease progression from asymptomatic early-stage to late-stage dementia, it is important to study various biomarkers (236).

The 24-hour EEG recording can be ideal possibility for predicting the progression of Alzheimer's disease, as it is a cheap, non-invasive diagnostic tool (237, 238). Considering the 1.5-times faster progression of cognitive decline in ACE in AD patients with SEA, the high prevalence of SEA observed in our study with 24-hour EEG recording is significant. Similar findings have been reported in another study, individuals with AD+SEA experienced a 2.5-times quicker fall in their yearly recorded MMSE scores than patients without SEA (119). Similarly to our results, this finding remained significant even after accounting for the effects of age, gender, and educational differences. We observed a smaller, 1.22 times faster reduction in MMSE scores among patients with SEA in our population. This may be explained by the fact that our cohort included older

patients who were receiving in a higher proportion of anti-dementia drugs. Differences between participants in the AD+SEA and AD-SEA groups in the two study samples may explain the slower progression of MMSE scores.

Several studies have shown that inflammatory molecules can be successful biomarkers in the diagnosis and progression of Alzheimer's disease (239, 240). The role of the gut microbiota in the pathogenesis and progression of Alzheimer's disease has also been investigated by several studies (241, 242). The oral microbiota and the inflammatory processes associated with periodontal disease can also influence the development and course of Alzheimer's disease, so dental prevention activities can also play an important role (243-245). APOE genotype may also play an important role in heterogeneity in the rate of cognitive decline in Alzheimer's disease (246). In addition, several studies have shown the cumulative effect of vascular risk factors on the progression of AD (247, 248). All these elements may have an impact on how AD progresses and draw attention to the importance of methodological differences between different studies (249).

A recent follow-up study with a large sample finds a link between circadian dysregulation and Alzheimer's progression, implying either a bidirectional relation or shared common underlying pathophysiological mechanisms (250). This finding may be consistent with our results, explaining that SEA predominantly (>90%) manifests during the sleep period.

In light of the above, further extended longitudinal clinical trials are needed to clarify the diagnostic and prognostic potential of EEG measurements as functional markers of AD at the individual level, taking into account a number of influencing factors. (251).

5.2.4. Limitations

Our study has several limitations. Firstly, since we didn't perform an EEG examination at the end of the follow-up, it is possible that the spike frequency and spatial distribution changed over that time. Even though all patients had structural MRI scan, a further major limitation is that the current investigation did not include positron emission tomography, cerebrospinal fluid analysis, or genetic testing. AD group was significantly older than the control group, however statistical analysis was adjusted for age. Patients'

co-morbidities and other drug therapies can affect both their cognitive performance and changes in it.

5.2.5. Clinical relevance and future directions

The strengths of our follow-up study were the careful patient selection with a relatively large number of patients, the long follow-up time, and the use and analysis of long-term EEGs that contain sleep-period. Our study highlights the importance of hyperexcitability (in form of SEA) in Alzheimer's disease, as it was detected in half of Alzheimer's patients. Since a significant proportion of cortical hyperexcitability can be detected during the sleep period, the use of 24-hour EEG recording is very important. Incorporation of 24-hour EEG recording to screen for cognitive decline and into care protocols should be considered. Our results suggest that the prevalence and the frequency of SEA are associated with the rate of cognitive decline in people with Alzheimer's disease. Information about the rapidity of disease progression can be crucial for both the patient and the family. Some study results suggest that it is possible that SEA may also play a role in the fluctuation of BPSD symptoms associated with the disease. This may also have an impact on the treatment of these symptoms and slow down the progression of the disease, thereby improving the quality of life of the people affected. This is already visible in the current ongoing drug trials. The study of hyperexcitability may be important not only for Alzheimer's disease but also for other neurodegenerative diseases. To further understand the significance of epileptiform activity in neurodegenerative illnesses, more research is needed.

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6. CONCLUSIONS

Our first study showed that in addition to the direct effects of the COVID-19 pandemic, the indirect effects are undoubtedly significant for the older generation, as the age group most at risk of the SARS-CoV-2 infection. These precisely concerned those lifestyle factors that may be the most protective factors against common diseases in old age, such as social and physical activity, wide access to health screening and checkups, adequate quality of sleep and good dietary habits. Our results show that time spent with family and close friends has decreased significantly, even as the use of digital services has increased dramatically. We found that physical immobility and reduced frequency of meeting with grandchildren were the most significant predictors of subjective cognitive impairment in the study population. Our findings highlight the significance of physical activity and close family relationships as a crucial aspect of healthy brain ageing that is typically disregarded.

In the second study we examined the importance of epileptiform discharges in patients without epileptic seizure. Using the 24-hour EEGs, we found that SEA are more common in AD patients than in control individuals. Temporal distribution of SEA showed that 65% of the discharges occur in stage 2 or deeper sleep, while analysis of spatial occurrence revealed strong left side dominance. We demonstrated that baseline occurrence of epileptiform discharges is associate with worse memory and visuospatial functions. We also found that individuals with SEAs show significantly faster progression of cognitive deterioration in a 3-year prospective examination of AD patients by repeated neuropsychological tests. Our EEG study highlights the importance of epileptiform activity in neurodegenerative disorders. Consideration should be given to including 24-hour EEG testing in the dementia investigation protocol. The role of epileptiform discharges in the pathomechanism of Alzheimer’s disease might serve as potential therapeutic target.

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In summary, our key findings the follows:

1. Pandemic-related restrictions had significant impact on the lifestyle, quality of life, mental and physical health of elderly people in Hungary.

2. Pandemic-related restrictions had detrimental effect on different levels of prevention in Hungary.

3. Physical immobility and social isolation are significant predisposing factors for subjective cognitive complaints.

4. Hyperexcitability (subclinical epileptiform activity) can be detected in half of Alzheimer's patients by 24-hour EEG monitoring.

5. In prospective follow-up, presence of hyperexcitability (subclinical epileptiform activity) significantly accelerates the progression of cognitive decline in patients with Alzheimer's disease.

6. 24-hour EEG examination is an ideal approach for detecting hyperexcitability in patients with Alzheimer's disease.

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7. SUMMARY

Due to the prominent incidence and increasing prevalence, diseases that cause cognitive decline in elderly lead a huge burden on society. The focus of dementia research is gradually turning toward prevention measures because in most cases there is currently no causative treatment for cognitive decline.

Our first study showed that, in addition to the direct impact of the COVID-19 pandemic on elderly over 60 years, the consequences of epidemiological measures and social changes surrounding them are also significant for this group. Our study suggests that the elderly experienced both a deterioration in their lifestyle and subjective quality of life, as well as that pandemic-related restrictions had a detrimental impact at different levels of prevention. We found that physical immobility and reduced frequency of time spent with grandchildren were the most important predictors of subjective cognitive complaints among those who did not have COVID-19 infection. Our study highlights the importance of early prevention and the relevance of modifiable risk factors for cognitive decline. Moreover, our results draw attention to the importance of physical activity and close family ties as key aspects of healthy brain ageing that are often overlooked.

In the second study, we investigated the use of 24-hour EEG testing in Alzheimer's disease. We found that the prevalence of the subclinical epileptiform activity is much higher in Alzheimer's patients than in controls. We demonstrated that Alzheimer’s patients with subclinical epileptiform activity have lower performance in the memory and visuospatial domains of Addenbrooke's Cognitive Examination. We also found that Alzheimer’s patients with epileptiform discharges show significantly faster progression of cognitive deterioration in a 3-year follow-up repeated by neuropsychological tests. Our EEG study highlights the importance of epileptiform discharges in neurodegenerative disorders and their progression. Further long-term EEG studies could lead to the development of diagnostic and therapeutic strategies for Alzheimer's disease.

It is still questionable which factors at the individual level play more important role in the onset, course, and progression of cognitive decline. Longitudinal studies may provide a way to understand the problem in more complex ways and to mitigate its impact.

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9. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

9.1. Publications related to the thesis

1. **Zsuffa, J. A.,** Katz S., Koszovacz, V., Berente, D. B., Kamondi, A., Csukly, G., Mangialasche, F., Rocha, A. S. L, Kivipelto, M., Horvath, A. A. (2024). Lifestyle and behavioural changes in older adults during the COVID-19 pandemic are associated with subjective cognitive complaints. Sci Rep, 14, 2502.
   https://doi.org/10.1038/s41598-024-52856-0
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2. **Zsuffa, J. A.,** Kalabay, L., Katz, S., Kamondi, A., Csukly, G., & Horvath, A.A. (2023). Care of dementia in the general practice. Orv Hetil, 164(32), 1263–1270.
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3. **Zsuffa, J. A**., Koszovacz, V., Berente, D. B., Balint, Z., Katz, S., Kamondi, A., Csukly, G., Horvath, A. A. (2022). Impact of the third wave of the covid pandemic on the lifestyle, mental and physical health of the Hungarian population over 60. Orv Hetil, 163(31), 1215-1223.
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4. Horvath, A. A., Papp, A., **Zsuffa, J**., Szucs, A., Luckl, J., Radai, F., Nagy, F., Hidasi, Z., Csukly, G., Barcs, G., Kamondi, A. (2021). Subclinical epileptiform activity accelerates the progression of Alzheimer's disease: A long-term EEG study. Clin Neurophysiol, 132(8), 1982-1989.
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9.2. Other publications

1. Frederick, H. J., Ziólkiewicz, O. A., **Zsuffa, J. A**., Horvath, A. A., Katz, S. (2023). Impact of the COVID-19 pandemic on the mental and physical health of Hungarian and foreign medical students studying in Hungary. Orv Hetil, 164(52), 2055–2064.
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2. Bolla, G., Berente, D. B., Andrassy, A., **Zsuffa, J. A**., Hidasi, Z., Csibri, E., Csukly, G., Kamondi, A., Kiss, M., Horvath, A. A. (2023). Comparison of the diagnostic accuracy of resting-state fMRI driven machine learning algorithms in the detection of mild cognitive impairment. Sci Rep, 13(1), 22285. https://doi.org/10.1038/s41598-023-49461-y
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3. Horvath, A. A., Berente, D. B., Vertes, B., Farkas, D., Csukly, G., Werber, T., **Zsuffa, J. A**., Kiss, M., Kamondi, A. (2022). Differentiation of patients with mild cognitive impairment and healthy controls based on computer assisted hand movement analysis: a proof-of-concept study. Sci Rep, 12(1), 19128. https://doi.org/10.1038/s41598-022-21445-4
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4. Berente, D. B., **Zsuffa, J.**, Werber, T., Kiss, M., Drotos, A., Kamondi, A., Csukly, G., Horvath, A. A. (2022). Alteration of Visuospatial System as an Early Marker of Cognitive Decline: A Double-Center Neuroimaging Study. Front Aging Neurosci, 14, 854368.
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5. **Zsuffa, J.,**, Torzsa, P., Előry, A., Kalabay, L. (2010). Management of metabolic syndrome in primary care. Journal of Hungarian family doctors, 3(2), 27-30.

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