UNIVERSITY OF MEDICINE AND PHARMACY

"CAROL DAVILA", BUCHAREST

DOCTORAL SCHOOL

FIELD OF MEDICINE

EFFECT OF APOLIPOPROTEIN ε4 ON PATIENTS WITH SUBJECTIVE COGNITIVE DECLINE

THESIS SUMMARY

PhD Supervisor:
PROF. UNIV. DR. TUDOSE CĂTĂLINA

PhD student: PAVEL ALEXANDRU-NECULAI

2023

Table of Contents

I. The general part

The general part of this PhD thesis includes a brief presentation of the global context of neurocognitive disorders followed by the description of subjective cognitive decline (SCD) with emphasize on the importance of genetic factors in cognitive function.

Currently, the global population is going through an aging phenomenon which will cause an increase in the prevalence of neurocognitive disorders (TNC). It is estimated that by the year 2050, the prevalence of Alzheimer's disease will increase 4 times compared to 2016 [1] .

At the moment there is no disease modifying treatment for Alzheimer's disease or most major neurocognitive disorders, but it has been found that certain interventions performed earlier (control of hypertension, diabetes, body weight, increased level of physical activity, use of a Mediterranean-style diet) can reduce the risk of developing Alzheimer's disease. For that reason, a part of the research has turned to detecting cognitive decline as early as possible. Mild Cognitive Impairment (MCI) is presently the earliest stage of cognitive decline from a clinical perspective. It is characterized by cognitive impairment which is noticeable when applying neuropsychological testing, but not sever enough to impair daily activities. Subjective cognitive decline occurs before the onset of objective symptoms of cognitive impairment, without impacting functionality [2].

The main topic of this thesis is subjective cognitive decline. The research diagnostic criteria for SCD are [2]:

a. Presence of subjective experience of cognitive decline compared to a previous level
b. Normal results in standardized tests used to assess the degree of cognitive impairment in existing neurocognitive disorders

The previously presented criteria were established by expert consensus in 2014 and since then SCD has become research topic with an increased need for expanding.

In 2020, following the accumulation of more information, the SCD-plus criteria were formulated [3]. These were developed following the discovery of more risk factors for cognitive decline from SCD to mild/major neurocognitive disorder. These are [3]:

a. The presence of cognitive decline in the memory domain regardless of subjective accusations being present in other cognitive domains as well
b. The onset of SCD symptoms within 5 years from the moment the person addresses a specialist

c. The patient must be at least 60 years old at onset of the subjective cognitive accusations
d. Presence of concern about SCD
e. Subjective cognitive symptoms are persistent over time
f. The patient seeks medical help in connection with the subjective cognitive symptoms
g. Cognitive decline is also declared by a caregiver

From a neurobiological point of view, there is evidence that people with SCD have abnormal deposits of beta-amyloid or tau proteins, cerebral atrophy and impaired neural connectivity. Also, the distribution pattern of amyloid deposits follows the same pattern as in Alzheimer's disease, respectively at the temporal, prefrontal medial level, anterior and posterior cingulate cortex, and in the precuneus [4]–[6][7], [8]. This is an argument that favors SCD as a prior stage to mild neurocognitive disorder.

Not all people with SCD will develop neurocognitive disorders over time. SCD is probably an extremely heterogeneous condition and many other causes can be associated with it, such as major depressive disorder, anxiety disorders, insomnia, pro-inflammatory status and certain personality traits. Therefore, precise identification (using clinical, socio-demographic, biological criteria - certain biological markers, brain imaging data, genetic data, etc.) of SCD cases that will develop into a neurocognitive disorder is essential, both for therapeutic and prognostic purposes.

The conditions most commonly associated with a lower risk of developing a major neurocognitive disorder in SCD persons are: reversibility of subjective cognitive symptoms, age under 50 years, absence of concern about cognitive symptoms, absence of a family history of Alzheimer's disease or other severe mental disorders (schizophrenia, bipolar affective disorder, major depressive disorder).

Subjective cognitive decline is noted by patients about 5 years before being diagnosed with mild neurocognitive disorder [9]. In other studies, subjective cognitive decline was present, on average, for 15 years before the diagnosis of Alzheimer's disease [10]. If SCD had a duration of more than 5 years and did not progress to a neurocognitive disorder, it can be considered, with increased probability, as stable, irreversible. The conversion rate from MCI to dementia is about 10% per year for [3] people in the community and between 16-18% for participants assessed in clinical trials. Differences [11][12] [13] in decline rate have been reported in literature, which advocates for the heterogeneity of this SCD. There may be a link between the type of cognitive domain affected and the risk of developing a

neurocognitive disorder. For example, impaired memory capacity significantly increases the risk of developing dementia compared to impaired social cognition.

Thus, SCD shows a high degree of heterogeneity in the general population. It may overlap with other psychiatric or medical disorders, substance use, physiological ageing, personality traits [14], [15]. Studies conducted so far have simultaneously analyzed groups of 2-3 risk factors associated with SCD.

The current paper is the first in this field to combine a large number of risk factors associated with SCD in order to bring further clarification to this concept, as well as its impact on cognitive functioning.

The apolipoprotein gene is the most common genetic risk factors involved in non-familial forms of dementia. Apolipoproteins are lipid transport proteins with role in the plasma cholesterol regulation and are encoded by a single gene [16] - *APOE*. The genotype of apolipoprotein E is one of the most powerful genetic determinants of Alzheimer's disease. It [17] has 3 common isoforms: ApoE2, ApoE3 and ApoE4. The presence of the E4 isoform significantly reduces the average age of onset of Alzheimer's disease [17].

It is known that ApoE4 is more frequently present in people who have neurocognitive disorders, but there are few studies which evaluate ApoE4 in people with SCD. A systematic review [18] showed that ApoE4 is infrequently present in the SCD group compared to controls, and that ApoE4 is also less often present in people with SCD compared to those who have been diagnosed with a neurocognitive disorder. There are also studies where the presence of ApoE4 has been correlated more frequently with the presence of a subjective cognitive decline. Thus, the current thesis takes a closer look at the role of ApoE4 within SCD, adding data to a topic that currently has contradictory results.

More recent genetic studies bring to attention single nucleotide polymorphisms (SNPs). They exert less effect on the overall risk of developing neurocognitive disorders compared to the *APOE* gene. One of the SNPs with increased likelihood of becoming a risk factor is rs2732703, a SNP located in the immediate vicinity of the MAPT gene [19]. It modulates intermolecular and intercellular interactions of various components within the immune system or other cellular types involved in the development of the central nervous system [20]. This thesis analyzes the effect of rs2732703 on SCD and cognitive function.

II. Personal contributions

The main objective of this thesis is to evaluate the differences in ApoE4 status between individuals with subjective cognitive decline and controls as well as its effect on cognitive functioning.

The secondary objectives focus on the impact of SCD on cognitive function, including all factors with a potential moderator role: socio-demographic characteristics, genetic status, somatic and psychiatric comorbidities, sleep quality, level of physical activity and personality traits.

The quality of life of the participants was also assessed to highlight how SCD affects this area.

Study design

The study had a cross-sectional design, with parallel groups and had a target of 100 participants included from the "Prof. Dr. Alexandru Obregia" psychiatric hospital and from community evaluated within the Memory Center. Participants included from the community were pre-screened by browsing the records of family doctors in the LifeMed clinic while they were making their routine visits. Patients who agreed to participate in the study were referred to the principal investigator (psychiatrist) who also led the assessments.

Participants were divided into two groups: a group with subjective cognitive decline and a control group (which does not exhibit subjective cognitive decline) in order to increase the significance of the results. Their evaluation included: *APOE* profile, respectively apolipoproteins E2, E3, E4 and SNP rs2732703 and tests for cognitive functioning, anxiety and depression, personality, quality of life, physical activity and sleep quality.

The study was conducted in accordance with the Helsinki Declaration and has the approval of the ethics committee of the Romanian Alzheimer's Society (no. 11/06.03.2020).

Evaluations

Subjective cognitive decline was evaluated with the following question: "Do you think you have troubles with your memory?", with the possible answers being: "Yes and it bothers me", "Yes, but it does not bother me" and "No, I do not consider that I have problems with my memory". Those who [21] responded with "Yes" were classified as having subjective cognitive decline, and those who responded with "No" in the control group. Cognitive function was evaluated using the following tests: Mini-Mental State Evaluation (MMSE), Rey Auditory Verbal Learning (RAVLT), Rey-Osterrieth complex figure, Trail Making Test (TMT) and Verbal Fluency Test (VFT). Quality of life and personality traits were evaluated

using: Short Form 36 (SF-36) and BIG Five. Physical activity was evaluated using the International Physical Activity Questionnaire (IPAQ) and the quality of sleep through the Pittsburg Sleep Quality Index (PSQI). The physical examination consisted in measuring the following parameters: systolic and diastolic blood pressure, heart rate, weight, height, abdominal circumference and calculation of the body mass index (BMI). The biological samples collected were: total cholesterol (used as a parameter for calculating the CAIDE risk score for dementia), HDL-cholesterol, LDL-cholesterol, blood glucose, *APOE* profile, rs2732703.

Participant selection

Participants must meet all the inclusion criteria and no exclusion criteria in order to be enrolled in the study.

Inclusion criteria:

1. Male or female, aged 50-80 years, who signs informed consent before initiating any procedure related to the study, and the participant is declared by the investigator as having the ability to understand the conditions necessary for participation in the study.
2. Presence of subjective memory complaints.
3. Participants with a score of at least 27 on MMSE.
4. Participants with a Maximum score of 9 on Functionality Assessment Questionnaire (FAQ).
5. Participants with a maximum score of 12 on the Hamilton scale of depression.
6. Participants with a maximum score of 17 on the Hamilton scale of anxiety.
7. No substance use (other than tobacco and coffee) in the last 6 months.

Exclusion criteria:

1. Cognitive or functional impairment severe enough to meet the criteria of dementia (major neurocognitive disorder) according to DSM 5/Alzheimer's Society.
2. Cognitive impairment severe enough to meet the criteria for mild neurocognitive disorder (MCI).
3. Participants with significant cerebral vascular disease, evaluated by Hachinski score greater than 4.
4. Participants currently diagnosed with intellectual disability (intellectual developmental disorder), major depressive disorder or any anxiety disorder.
5. Participants with severe somatic conditions (heart failure, chronic renal failure, respiratory failure, heart rhythm disturbances).

6. Participants diagnosed with severe neurological conditions (e.g. Parkinson's disease, epilepsy).

Statistical analysis

The statistical processing of the data was done using the SPSS Statistics v26 software. Descriptive statistics were used to characterize the sample. Statistical analysis was performed using Chi-Square tests for categorical variables and Student-t test (Mann-Whitney for nonparametric variables) for continuous variables. Covariation analysis was applied to assess the role of moderators. The statistical significance was established $p<0.05$.

ApoE4 status and cognitive functioning in middle-aged and elderly patients

ApoE4 is one of the most important genetic risk factors for cognitive decline. The purpose of this study was to examine the effect of ApoE4 on cognitive function in a group of people who did not have cognitive impairment at the time of inclusion.

51 participants were included, 11 (21.57%) were ApoE4 positive (ApoE4+) and 40 (78.43%) were ApoE4 negative (ApoE4- or control group).

The group was matched for the main demographic characteristics that could have represented moderator factors (age, sex, educational level), an important aspect especially in a study designed to evaluate cognitive function as a primary outcome.

The ApoE4+ participants had significantly lower scores on the Rey complex figure test – memory part (p=.019), with no significant differences in the copying part (p=.275). ApoE4+ patients had lower scores on all trials of the RAVLT test – Trial 1 (p=.342), Trial 5 (p=.095), Total (p=.101), Trial 6 (p=.328), Delay (p=.231) and Recognition (p=.085) compared to ApoE4-, but the differences did not reach statistical significance. There were no statistically significant differences between the ApoE4+ and ApoE4- groups in terms of MMSE (p=.553), TMT A (p=.261), TMT B (p=.828) and VFT (p=.779) scores. ApoE4 was not more prevalent in the SCD group.

These results are consistent with literature data. ApoE4+ people have a poorer objective cognitive performance than ApoE4-, but insufficiently severe to diagnose a neurocognitive disorder [22]. These changes are most commonly highlighted in the field of attention and memory.

In the present group, ApoE4+ people had an impaired visuo-spatial memory. This could be an important argument to closely monitor these participants, as they could be the group at the highest risk of developing a neurocognitive disorder.

At the moment, it is not useful to apply screening for ApoE4 in the general population because, even if the results are positive, the overall risk must be carefully considered together

with other potential risk factors. Also, finding out that one has a positive result could cause anxiety or even depression. It is important the result is delivered by a specialist who can perform both a form of psychoeducation and counseling.

This type of investigation could become part of a battery of evaluations of a person over 50 years who develops SCD, especially because such genetic testing has become more accessible both financially and in terms of the availability of testing centers. After the diagnostic criteria for SCD were established, further studies found that patients within this group also had subtle objective cognitive complaints yet not severe enough to warrant the diagnosis of mild cognitive impairment.

Is there room for objective cognitive impairment within subjective cognitive decline?

For this study, total sample initially included was 110 participants. After carrying out the matching procedure and excluding participants with incomplete data, 101 participants were included in the final analysis. 66.33% (n=67) had SCD and 33.66% (n=34) remained in the control group. The groups were matched by gender, age, education and MMSE score.

The analysis of socio-demographic and clinical variables showed that people with SCD had a more frequent personal pathological history of depression compared to the control group.

The SCD group had a worse performance of auditory-verbal memory, in all trials of the RAVLT except for the Recognition test where the average scores were equal between groups – 14 (p=.95). However, statistically significant differences only existed in Trial 1 (p=.021) and total score (p=.023). Both groups obtained the maximum scores in the Rey complex figure test, for the copying task– 36, and for the memory task the SCD group had a lower score, but this difference was not statistically significant (p=.439).

Participants with SCD had lower scores compared to the control group when evaluating executive function with the help of TMT. The median score for the TMT A test in the SCD group was 56 seconds compared to the control group where the median was 47 seconds (p=.012). The TMT B median score in the SCD group was 131 seconds and 113 seconds in the control group, not representing a statistically significant difference (p=.138).

The SCD group showed a decreased verbal fluency averaging a total score of 31.93 compared to the control group – 33.97, but the difference was not statistically significant (p=.421).

While evaluating personality traits, there were statistically significant differences between the groups regarding the Negative Emotion Trait (p=.043). Participants in the SCD

group had a higher score – 14.37 (±4.15) compared to the control group – 12.64 (±3.68), resulting in the SCD group expressing more Negative Emotion. There were no statistically significant differences in features such as Extraversion (p=.488), Agreeableness (p=.753), Conscientiousness (p=.971) or Openness (p=.779). There were no statistically significant differences (p=.917) between the average scores of the IPAQ (physical activity), although the SCD group showed a higher level of physical activity compared to the control group. There were no statistically significant differences between the groups in terms of sleep quality (p=.438).

In order to evaluate the effect of each statistically significant variable individually (negative emotion, personal history of depression, RAVLT Trial 1, RAVLT Total and TMT A) a logistical regression was performed and the personal history of depression was the only variable that retained its statistical significance.

People with SCD presented, more emphatically, the personality trait of Negative Emotion. This trait predisposes people to react more frequently with symptoms of anxiety, sadness, depression to stressors, compared to those who do not express this trait. This association has been described in literature, but it cannot be stated whether this trait is a consequence or a cause of SCD. Participants with SCD have diminished memory and attention capacity compared to the control group. This may represent common ground with neurocognitive disorders. Another possible explanation would be that the SCD group had performance anxiety, an argument supported by the worse performance in the first trials (for example within RAVLT) and with improvements as the test progresses, in the end approaching the same results as the control group.

To date, SCD has not been stratified according to the presence/absence or even degree of objective cognitive impairment, and the results obtained in this study advocates for refining the current diagnostic criteria of SCD. It is possible to include SCD without objective cognitive decline and, respectively, SCD with objective cognitive decline within the cognitive continuum.

If SCD proves to be the first stage of the cognitive continuum, it could become an increasingly important area for the implementation of prevention strategies and further research should consider interventions that can be administered starting from this stage.

Screening for SCD should begin from the first contact of the person with the doctor. One can apply the screening question for SCD used in this study, being quick and effective: "Do you think you have memory problems?". People who consider themselves as memory impaired could be forwarded to memory centers for detailed assessments and the possibility

of being taken into account for closer monitoring. Surely stratifying the risk of developing dementia will be an important point in the near future. As research advances, other elements (dosing of amyloid or tau protein) could be added that, in the end, the detection of a specific group of patients - those at the highest risk of developing a neurocognitive disorder, will be optimized.

Non-pharmacological interventions such as cognitive training or cognitive improvement may also be administered to the SCD group that has objective cognitive impairment. These interventions can be customized to help the participant make improvements precisely in the affected cognitive domains, which have been identified after detailed evaluations. Non-pharmacological interventions such as cognitive training can become the first form of treatment for patients at risk of developing a neurocognitive disorder.

In order to eliminate the possibility of a person having false positive test due to performance anxiety, a form of brief supportive therapy can be performed before the start of the evaluation process. People with performance anxiety might have a higher prevalence of Negative Emotion. In this case, we can consider excluding these participants in future studies to better control for anxiety as a moderating factor for cognitive functioning. Offering these participants a psychotherapeutic intervention could relieve their performance anxiety and improve their quality of life.

Cognitive assessment of patients with subjective cognitive decline stratifying after the presence of the level of concern about these symptoms

The hypothesis of this study was that people who have subjective cognitive decline and show concern about these symptoms will experience a more pronounced objective cognitive impairment compared to those who do not show concern and, respectively, to the control group (those who responded with "No").

101 participants were included in the final analysis. 49.5% answered with "Yes and it bothers me", 16.83% answered with "Yes, but it does not bother me" and 33.67% answered with "No".

The groups were matched and there were no statistically significant differences in terms of sex, educational level, background, BMI, hypertension, type II diabetes mellitus, other somatic comorbidities, treatment for somatic comorbidities, FAQ, anxiety, physical activity or sleep quality.

There were statistically significant differences between people with SCD who worry about their symptoms and the control group in terms of RAVLT Trial 1 (p=.044), RAVLT Trial 5 (p=.047), and RAVLT Total (p=.017) scores. There were also statistically significant

differences between the SCD group that does not show concern about symptoms and the control group regarding the RAVLT Trial 1 score (p=.047). There were no statistically significant differences between the SCD and control groups regarding the Rey complex figure test.

There were statistically significant differences between the SCD group showing concern and the control group (p=.035), but also differences between the SCD group without concern and the control group (p=.020) in executive functioning assessed with TMT A. The worst performance was in the SCD group without concern (63 sec), followed by the SCD group showing concern (55 sec) and then the control group (47 sec). There were no statistically significant differences between the SCD groups and control regarding VFT scores.

Although the median Hachinski scores of the 3 groups were equal, there was a statistically significant difference between the group with concern about SCD symptoms and the control group (p=.028), most likely due to differences in interquartile intervals.

People expressing concern about SCD symptoms had a higher HAM-D score but the difference was clinically insignificant.

People with SCD who show concern about symptoms have increased Negative Emotion compared to the control group (p=.017). There were no within-group significant differences in terms of other personality traits.

Evaluation of cognitive status according to rs2732703 status

To date, the prevalence of rs2732703 in people with SCD has not been studied. A total of 51 participants were enrolled. 22 participants (43.1%) presented rs2732703. In both groups, there were more female participants (79.3% in the rs2732703 negative group compared to 81.8% in the rs2732703 positive group). The mean age was 63.68 years in the rs2732703 group and 65.9 years in the control group.

There were no statistically significant differences between the rs2732703 groups in terms of SCD status, RAVLT trials, Rey complex figure test, TMT test and verbal fluency test scores.

There were no statistically significant differences between rs2732703 groups in terms of socio-demographic and clinical data except for BMI. The rs2732703 group had a significantly lower BMI compared to the control group – p=.015. This was moderated by the more intense physical activity of the rs2732703 group.

Studies involving SNPs, especially Genome Wide Association Studies (GWAS), represent a potential research starting point for detecting neurobiological models of disease. Following the pattern of other psychiatric disorders (such as schizophrenia), it would be

important to study SNPs in cohorts of patients with neurocognitive disorders. If SNPs are detected in people with neurocognitive disorders, one can later explore the phenotypic manifestations, thus reaching new explanations of the neurobiological mechanisms of cognitive impairment.

Caide score assessment (dementia risk) in positive ApoE4 individuals compared to negative ApoE4

The Cardiovascular Risk Factors, Ageing and Dementia Score (CAIDE) was developed as a screening tool for neurocognitive disorders. The purpose of this study is to see if there is a difference between ApoE4 status and the CAIDE score and the influence of this score on cognitive function.

There was no statistically significant difference between the ApoE4 groups and the CAIDE score (p=.502). Participants with higher CAIDE scores had significant impairment in attention and short-term memory, similar to participants with SCD.

The effect of personality traits on subjective evaluation of memory

Personality traits were evaluated using the BIG FIVE questionnaire which presents 5 areas: Extraversion, Agreeability, Conscientiousness, Negative Emotion and Openness. Higher scores represent increased expression of a personality trait. People with SCD also express more Negative Emotion compared to control group (p=.042).

Evaluation of cognitive function by status of SCD and ApoE4

For this study, 4 groups of participants were created: ApoE4+ and SCD +, ApoE4+ and SCD -, ApoE4- and SCD +, ApoE4- and SCD -. There were no statistically significant differences between the groups in terms of objective cognitive assessment measured by MMSE, RAVLT, Rey complex figure, TMT A and B and VFT.

Quality of life of people with subjective cognitive decline

Literature states that people with SCD have a lower quality of life compared to controls, especially regarding physical function, vitality and emotional function on the SF-36 questionnaire. Most of the time, quality of life in studies with SCD was evaluated in patients who had somatic or psychiatric comorbidities, making it difficult to assess which factor had a greater impact on quality of life [23].

The SF-36 questionnaire evaluates 8 areas: physical function, pain, role-limitation of physical and emotional function, emotional well-being, social functioning, energy and general perception of health. Higher scores in each area represents a better quality of life.

A total of 110 patients were included. After the matching procedure for age, sex, education and MMSE score, 101 patients were included in the final analysis. Of these, 66.3% were in the SCD group (n=67) and 33.7% (n=34) in the control group.

The control group had a significantly better quality of life in terms of physical functioning compared to the SCD group (p=.034).

Furthermore, SCD participants had a lower quality of life compared to the control group (p=.010) in terms of the Role-Limitation of the Physical Function. Although the medians of the Emotional Function scale were equal (100) there were significant differences between the interquartile intervals between the two groups, 66.67-100 in the SCD group, respectively 100-100 in the control group (p=.019).

Participants with SCD show significantly lower levels of energy compared to controls (p=.018). Because the SCD group also expressed more Negative Emotion compared to controls, a logistic regression was performed to assess if personality traits determine quality of life. The result was negative, concluding that SCD was the variable causing a lower quality of life and that this effect was not moderated by the presence of Negative Emotion.

Because SCD impacts quality of life, rapid development of useful interventions in reducing symptomatology is necessary. However, until effective interventions for symptom reduction are developed, people with SCD may benefit from non-pharmacological interventions such as supportive therapy or cognitive-behavioral therapy. These interventions may offer an improvement in quality of life by developing appropriate coping mechanisms.

Factors that affect quality of life in people aged 50-80 years

The objective of this study was to evaluate predictors of quality of life in people aged 50-80 years. A total of 110 participants were enrolled, and after the elimination of those who did not complete all questionnaires, 103 participants were included in the final analysis. Of these, 24 were in the group with an increased quality of life, 54 in the group with a moderate quality of life and 25 in the group with a low quality of life.

Better quality of life from a physical point of view was positively correlated with: lower age (p=.003), increased educational level (p=.044), increased economic status (p=.011), being employed (p=.028), being in a relationship (p=.033), a reduced BMI (p=.029), compliance with treatment for somatic comorbidities (p=.035), the presence of extraversion (p=.039) and conscientiousness (p=.044) as personality traits, a high level of physical activity (p=.009), better sleep quality (p=.008) and better overall cognitive functioning (p=.023).

The predictive factors for a better quality of life from a mental health point of view were: the absence of depressive symptoms (p=.020), conscientiousness (p=.012) and the absence of negative emotion (p<.001) and better sleep quality (p=.001).

Interventions such as psychotherapy can have a positive effect on quality of life by modifying the above mentioned risk factors. For example, alleviating negative emotion personality trait can be achieved through cognitive-behavioral psychotherapy sessions. Another example would be applying a motivational interview to increase adherence to a regular exercise schedule. Insomnia can also be approached with the help of psychotherapy, first of all by using sleep hygiene techniques such as: lying down and waking up at the same hours, ingestion of the last meal at least 2 hours before bedtime, reducing the time spent on electronic devices before bedtime or through more complex cognitive-behavioral therapy sessions. In the treatment of insomnia there are also pharmacological approaches such as: benzodiazepines, antidepressants or low-dose antipsychotics. Also, through psychotherapeutic interventions one can develop healthy coping mechanisms when there is no progress in terms of modifying personality traits.

7. Conclusions and personal contributions

In this thesis, all the proposed objectives have been evaluated, obtaining both positive and negative results.

People with SCD had lower objective cognitive performance especially in the attention domain. This difference was more obvious within the subgroup that also has concerns about SCD symptoms.

People with at least one ApoE4 allele had lower objective cognitive performance compared to ApoE4 negative participants (without any ApoE4 allele), with increased impairment in visual memory.

There was no statistically significant difference in ApoE4 status within the SCD group compared to the control group. Evidence in literature is mixed with respect to this association and it may only be a coincidence determined by neuropathological similarities between each individual entity. Currently, we do not have sufficient evidence to consider ApoE4 a risk factor for SCD, but both SCD and ApoE4 are individual and cumulative risk factors for the development of a neurocognitive disorder.

Participants with higher CAIDE score had attentional deficits and impairments in short-term memory.

People with SCD had a lower quality of life compared to the control group in terms of physical functioning, role-limitation due to physical and emotional problems and reported lower energy levels.

Although the SCD group expressed more Negative Emotion compared to the control group, this did not significantly influence the cognitive performance of the participants.

The SNP rs2732703 did not impair cognitive function of the participants, nor the SCD status. There were also no significant differences between the SCD group and control in terms of sleep quality and physical activity.

The originality of the current thesis consisted in the simultaneous inclusion, for the first time in literature, of a large number of risk factors that influence cognitive function: socio-demographic and clinical factors, ApoE4, rs2732703, personality traits, quality of sleep and level of physical activity. This is important to elucidate whether subjective cognitive decline itself causes an objective cognitive impairment or this effect is moderated by other factors. Also, looking at all these factors from as a whole, one can draw additional conclusions to those presently existent in the literature about the characteristics of subjective cognitive decline.

From the studies undertaken, participants with SCD had poorer cognitive performance, but not severe enough to be diagnosed with mild neurocognitive disorder. It is possible that this subgroup consists of people with the highest risk of developing a neurocognitive disorder. This, however, will be clarified by performing a longitudinal study.

It is also possible that SCD might represent the first stage within the cognitive continuum. If further studies confirm this, it could become a potential target for disease modifying drugs. Precisely identifying people with SCD who will later progress to a neurocognitive disorder is a fundamental element for treatment and prognosis. In order to achieve this, we must also be able to better identify the risk factors for SCD (using clinical, socio-demographic, biological-certain biological markers, brain imaging data, genetic data, etc.). Thus, it will be possible to develop curative therapeutic interventions that will significantly change the evolution of the disease (a fundamental aspect for patients and their families, for professionals and as well as for policy makers).

A group of people with SCD will not develop neurocognitive disorders. It is necessary to establish what causes their subjective cognitive decline. It is possible that SCD represents a functional neurologic disorder or a category of transdiagnostic symptoms. These people may present subjective cognitive complaints as manifestations of affective, personality or sleep disorders that have either not yet been diagnosed or persist after the remission of aforementioned disorders.

It is important for clinical practice to increase the level of awareness of subjective cognitive decline among patients and professionals. In research, there is a need to refine the the diagnostic criteria for SCD and develop a risk score that will be able to identify people with SCD at risk for neurocognitive disorders, which represent a target group for future therapeutic interventions.

Selective bibliography

[1] A. Brookmeyer, E. Johnson, K. Ziegler-Graham, and H. M. Arrighi, "Forecasting the global burden of Alzheimer's disease," *Alzheimer's and Dementia*, vol. 3, no. 3, pp. 186–191, 2007, doi: 10.1016/j.jalz.2007.04.381.

[2] f. Jessen *et al.* , "A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease," *Alzheimer's and Dementia*, vol. 10, no. 6, pp. 844–852, 2014, doi: 10.1016/j.jalz.2014.01.001.

[3] f. Jessen *et al.* , "The characterisation of subjective cognitive decline," *Lancet Neurol*, vol. 4422, no. 19, pp. 1–8, 2020, doi: 10.1016/S1474-4422(19)30368-0.

[4] L. A. Rabbi, C. M. Smart, and R. E. Amariglio, "Subjective Cognitive Decline in Preclinical Alzheimer's Disease," *Annu Rev Clin Psychol*, vol. 13, pp. 369–396, May 2017, doi: 10.1146/ANNUREV-CLINPSY-032816-045136.

[5] Y. Sun, F. C. Yang, C. P. Lin, and Y. Han, "Biochemical and neuroimaging studies in subjective cognitive decline: progress and perspectives," *CNS Neurosci Ther*, vol. 21, no. 10, pp. 768–775, Oct. 2015, doi: 10.1111/CNS.12395.

[6] S. Lista *et al.* , "Evolving Evidence for the Value of Neuroimaging Methods and Biological Markers in Subjects Categorized with Subjective Cognitive Decline.," *J Alzheimers Dis*, vol. 48 Suppl 1, no. S1, pp. S171-91, Sep. 2015, doi: 10.3233/JAD-150202.

[7] B. E. Snitz *et al.* , "Amyloid-beta imaging in older adults presenting to a memory clinic with subjective cognitive decline," *J Alzheimers Dis*, vol. 48, no. 0 1, p. S151, Sep. 2015, doi: 10.3233/JAD-150113.

[8] A. Perrotin, E. C. Mormino, C. M. Madison, A. O. Hayenga, and W. J. Jagust, "Subjective cognition and amyloid deposition imaging: a Pittsburgh Compound B positron emission tomography study in normal elderly individuals," *Arch Neurol*, vol. 69, no. 2, pp. 223–229, Feb. 2012, doi: 10.1001/ ARCHNEUROL.2011.666.

[9] R. J. Caselli *et al.* , "Subjective cognitive decline: Self and informant comparisons," *Alzheimer's and Dementia*, vol. 10, no. 1, pp. 93–98, 2014, doi: 10.1016/j.jalz.2013.01.003.

[10] B. Reisberg, "Dementia: a systematic approach to identifying reversible causes," *Geriatrics*, vol. 41, no. 4, p. 30—46, Apr. 1986.

[11] M. Bruscoli and S. Lovestone, "Is MCI really just early dementia? A systematic review of conversion studies," *Int Psychogeriatr*, vol. 16, no. 2, pp. 129–140, 2004, doi: 10.1017/s1041610204000092.

[12] A. Kluger, S. H. Ferris, J. Golomb, M. S. Mittelman, and B. Reisberg, "Neuropsychological prediction of decline to dementia in nondemented elderly," *J Geriatr Psychiatry Neurol*, vol. 12, no. 4, pp. 168–179, 1999, doi: 10.1177/089198879901200402.

[13] B. Reisberg, M. B. Shulman, C. Torossian, L. Leng, and W. Zhu, "Outcome over seven years of healthy adults with and without subjective cognitive impairment,"

Alzheimer's and Dementia, vol. 6, no. 1, pp. 11–24, 2010, doi: 10.1016/j.jalz.2009.10.002.

[14] J. L. Molinuevo *et al.* , "Implementation of subjective cognitive decline criteria in research studies," *Alzheimer's and Dementia*, vol. 13, no. 3, pp. 296–311, 2017, doi: 10.1016/j.jalz.2016.09.012.

[15] J. A.F. *et al.* , "Memory complaints in a community sample aged 60-64 years: Associations with cognitive functioning, psychiatric symptoms, medical conditions, APOE genotype, hippocampus and amygdala volumes, and white-matter hyperintensities," *Psychol Med*, vol. 34, no. 8, pp. 1495–1506, 2004, doi: http://dx.doi.org/10.1017/S0033291704003162.

[16] R. W. Mahley, T. L. Innerarity, S. C. Rall, and K. H. Weisgraber, "and function," vol. 25, 1984.

[17] Y. Chen, M. S. Durakoglugil, X. Xian, and J. Herz, "ApoE4 reduces glutamate receptor function and synaptic plasticity by selectively impairing ApoE receptor recycling," no. 13, 2010, doi: 10.1073/pnas.0914984107.

[18] A. JI, S. CM, and G. JR, "Subjective Cognitive Decline and APOE ε4: A Systematic Review," *J Alzheimers Dis*, vol. 65, no. 1, pp. 303–320, 2018, doi: 10.3233/JAD-180248.

[19] G. Jun *et al.* , "ORIGINAL ARTICLE A novel Alzheimer disease locus located near the gene encoding tau protein," pp. 1–10, 2015, doi: 10.1038/mp.2015.23.

[20] G. Giannuzzi *et al.* , "Evolutionary dynamism of the primate LRRC37 gene family," *Genome Res*, vol. 23, no. 1, pp. 46–59, Jan. 2013, doi: 10.1101/GR.138842.112.

[21] f. Jessen *et al.* , "A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease," *Alzheimer's and Dementia*, vol. 10, no. 6, pp. 844–852, Nov. 2014, doi: 10.1016/j.jalz.2014.01.001.

[22] G. A. Rodriguez, M. P. Burns, E. J. Weeber, and G. W. Rebeck, "Young APOE4 targeted replacement mice exhibit poor spatial learning and memory, with reduced dendritic spine density in the medial entorhinal cortex," *Learning & Memory*, vol. 20, no . 5, pp. 256–266, 2013, doi: 10.1101/LM.030031.112.

[23] G. Pusswald *et al.* , "Health-Related Quality of Life in Patients with Subjective Cognitive Decline and Mild Cognitive Impairment and its Relation to Activities of Daily Living," *Journal of Alzheimer's Disease*, vol. 47, no. 2, pp. 479–486, Jul. 2015, two: 10.3233/JAD-150284.

List of published works

Full papers published in Web of Science journals

1. **A.-N. Pavel**, R. M. Paun, V. P. Matei, I. Dutu, and C. Tudose, "APOE4 STATUS AND COGNITIVE FUNCTION IN MIDDLE-AGED AND ELDERLY PEOPLE," *Balkan Journal of Medical Genetics*, vol. 25, no. 1, pp. 13–18, 2022, doi: 10.2478/bjmg-2022-0012. - http://www.bjmg.edu.mk/UploadedImages/pdf/bjmg-2022-0012.pdf
2. **A. Pavel**, V. Matei, P. Radu, and C. Tudose, "How 'subjective' is subjective cognitive decline?," *Psychiatry Clin Psychopharmacol*, vol. 32, no. 4, pp. 299–305, 2022, doi: 10.5152/pcp.2022.22506. https://psychiatry-psychopharmacology.com/en/how-subjective-is-subjective-cognitive-decline-133192

Full papers published in journals indexed in PubMed

1. **A. Pavel**, R. Paun, M. Mihalcea, I. Dutu, C. Tudose, and A. Obregia, "Maedica-a Journal of Clinical Medicine Cognitive Differences in Subjective Cognitive Decline with and without Associated Worry Cognitive DifferenCes in sCD," *Maedica A Journal of Clinical Medicine*, vol. 17, no. 4, p. 2022, 2022, doi: 10.26574/maedica.2022.17.4.7
   https://www.maedica.ro/articles/2022/4/2022_17(20)_No4_pg771-776.pdf

Abstracts published in Web indexed journals of Science

1. Apolipoprotein E4 and cognitive evaluation in unimpaired adults. **A. Paul** 1, V. Matthew 1, R. Peacock 1, C. Tudose 1. 2022, Neuroscience Applied (1) https://doi.org/10.1016/j.nsa.2022.100544
2. Is there any room for objective cognitive impairment in subjective cognitive decline? **A. Paul** 1, V. Matthew 1, R. Peacock 1, I. Dutu 1, C. Tudose 1. 2022, Neuroscience Applied (1). https://doi.org/10.1016/j.nsa.2022.100325