Dement Geriatr Cogn Disord Extra 2018;8:439–452

Dementia and Geriatric Cognitive Disorders

DOI: 10.1159/000493749
Received: May 15, 2018
Accepted: September 13, 2018
Published online: November 28, 2018

Original Research Article

Lifestyle Factors Are Important Contributors to Subjective Memory Complaints among Patients without Objective Memory Impairment or Positive Neurochemical Biomarkers for Alzheimer's Disease

Anna Miley-Akerstedt[a, b] Vesna Jelic[c, d] Kristina Marklund[d] Håkan Walles[c, d] Torbjörn Åkerstedt[a, e] Göran Hagman[c, d] Christin Andersson[a, d]

[a]Department of Clinical Neuroscience, Karolinska Institute, Solna, Sweden; [b]Division of Medical Psychology, Karolinska University Hospital, Solna, Sweden; [c]Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Solna, Sweden; [d]Department of Aging, Karolinska University Hospital, Solna, Sweden; [e]Stress Research Center, Stockholm University, Stockholm, Sweden

Keywords

Subjective memory impairment · Subjective cognitive impairment · Stress · Sleep · Preclinical dementia · Memory clinic · Mild cognitive impairment · Cognition · Neuropsychology · AB_{42}

Abstract

Background/Aims: Many patients presenting to a memory disorders clinic for subjective memory complaints do not show objective evidence of decline on neuropsychological data, have nonpathological biomarkers for Alzheimer's disease, and do not develop a neurodegenerative disorder. Lifestyle variables, including subjective sleep problems and stress, are factors known to affect cognition. Little is known about how these factors contribute to patients' subjective sense of memory decline. Understanding how lifestyle factors are associated with the subjective sense of failing memory that causes patients to seek a formal evaluation is important both for diagnostic workup purposes and for finding appropriate interventions and treatment for these persons, who are not likely in the early stages of a neurodegenerative disease. The current study investigated specific lifestyle variables, such as sleep and stress, to characterize those patients that are unlikely to deteriorate cognitively. ***Methods:*** Two hundred nine patients (mean age 58 years) from a university hospital memory disorders clinic were included. ***Results:*** Sleep problems and having much to do distinguished those with subjective, but not objective, memory complaints and non-pathological biomarkers for Alzheimer's

Dr. Anna Miley-Akerstedt
Department of Clinical Neuroscience, Karolinska Institute
Nobels väg 9
SE–171 65 Solna (Sweden)
E-Mail anna.miley.akerstedt@ki.se

disease. ***Conclusions:*** Lifestyle factors including sleep and stress are useful in characterizing subjective memory complaints from objective problems. Inclusion of these variables could potentially improve health care utilization efficiency and guide interventions.

Introduction

Dementia, or major neurocognitive disorder, is characterized by a significant cognitive and functional decline [1] and afflicts 47 million individuals worldwide, 50–70% of whom suffer from Alzheimer's disease (AD) [2]. The diagnosis of dementia is, in part, based on neuropsychological testing demonstrating impaired cognition [1]. However, there are also early neuropathological changes that occur several years before neuropsychological deficits appear. These changes can be detected by neurochemical biomarkers and, as they appear many years before a dementia diagnosis [3, 4], have been used as a means of early detection. The common neurochemical biomarkers for Alzheimer's dementia include amyloid-β (AB_{42}), phosphorylated τ (p-τ,) and total τ (t-τ) [5], with AB_{42} possibly being a better predictor – relative to t-τ and p-τ – *early* in the degenerative process [6].

The societal costs for dementia care are high. In Sweden, the cost for the dementia health care system is similar to that of the combined costs for cancer and heart disease [7]. When considering the costs of the diagnostic workup, a recent paper by Wimo et al. [8] estimated that evaluation of a single patient at a specialist clinic (e.g., memory disorders clinic) costs approximately SEK 12,095 (USD 1,400) and that annual costs of diagnostic workups in Sweden are approximately SEK 240 million (USD 40 million). Moreover, the description of Wimo et al. [8] of recent data from the Swedish Dementia Registry (SveDem) suggests that only approximately 50% of those who undergo a dementia workup are actually diagnosed with a form of dementia. In fact, 38% of patients who turn up for evaluation at memory disorder clinics are classified as having subjective cognitive impairment (SCI) [9]. These individuals do not show impaired performance on neuropsychological testing that would warrant a diagnosis of cognitive impairment, and most of them do not have pathological biomarkers in their cerebrospinal fluid (CSF) that would indicate a neurodegenerative process [9].

The terms SCI and subjective cognitive decline (SCD; the two terms are used interchangeably in this study when referring to previous research) are rather unspecific, as cognitive complaints can exist for a variety of reasons other than a neurodegenerative disease. For the purpose of research on this particular patient group, the Subjective Cognitive Decline Research Initiative (SCD-I) has proposed that individuals who are categorized as having SCD should have no objective indicator of cognitive impairment (i.e., no decline on neuropsychological tests) [10].

Despite SCI not being associated with cognitive decline at the time of testing, there is an ongoing discussion on whether or not it may be a risk factor for later cognitive decline. The evidence is mixed; some studies have found it to be a risk factor for mild cognitive impairment (MCI) and/or a dementing disorder such as AD [11, 12], while other studies have found subjective complaints to be a benign condition with little risk for future cognitive decline, even at a 6-year follow-up [13]. There is not yet a consensus in the literature on whether SCI, itself, constitutes an early marker for future cognitive decline and/or dementia.

Therefore, the SCD-I group has created a framework of criteria that may identify individuals with subjective complaints who are at risk for future cognitive decline or dementia, who are categorized as SCD plus [10]. These criteria include a subjective sense of memory decline (as opposed to other cognitive domains), an onset of subjective decline within the last

5 years, an age of onset of complaints older than 60 years, feeling worried about SCD, and feeling worse relative to same-aged peers [10].

While awaiting conclusive data on SCI as a possible risk factor of dementia, early detection of SCI would be valuable in any efforts to spare individuals and the healthcare system the labor-intensive and costly cognitive/biological workup at a memory clinic. A few recent studies have investigated which cognitive factors may identify and differentiate individuals with SCI from those with MCI or dementia [14, 15]. When considering cognitive symptoms as a means of predicting future cognitive decline in the SCI population, however, the results have been mixed. For example, low memory performance at baseline cognitive testing predicted conversion to MCI in individuals categorized as SCI plus (according to the SCI-I), as compared to SCI and individuals without cognitive complaints [16]. Moreover, diminished psychomotor speed and language performance have differentiated SCI individuals from participants without cognitive complaints [17]. In contrast, a study by Hessen et al. [18] found that lower baseline scores on memory tests did not significantly predict individuals who declined cognitively at the 2-year follow-up from those who did not. Moreover, performance on semantic memory tests did not differentiate individuals with SCI from healthy controls [14]. Indeed, the SCI research initiative has suggested that in the preclinical stages it may be especially difficult to detect subtle cognitive changes, as an individual may still be able to compensate for any difficulties during cognitive testing [10]. This would suggest that variables in addition to cognitive test results might be important for early identification of those unlikely to progress.

One explanation for the different findings in the literature on SCI could be that the mean age of the patients included in the studies varies greatly. For example, studies that have found weaker to no associations between biomarker variables, cognitive variables, and a risk for cognitive decline to MCI or dementia appear to have included younger participants with a mean age <63 years [13, 18]. In contrast, studies that have found SCI to be a significant risk factor for future dementia have had a higher mean age (over 70 years) among the patients [15–17]. Hessen et al. [18] suggested that the difference in prognostic outcomes between studies examining biomarkers and cognition could potentially be explained by the age at baseline.

Apart from biological and/or cognitive indicators of decline, many studies of individuals with subjective cognitive complaints have also focused on lifestyle variables, such as stress and emotional functioning [19, 20]. Higher ratings of cognitive complaints have been found to be associated with more depressive symptoms, independently of AB_{42} levels, in healthy older adults [20]. Furthermore, both stress and depressive symptoms are more common in individuals with subjective cognitive complaints [21] as compared to individuals with MCI [19]. Eckerström et al. [19], however, focused only on stress that was experienced as negative by the patient. Possibly, apart from negative stress, factors like work overload or "having too much on one's plate" may be of interest. In other words, being overloaded with duties, activities, or social engagements can be cognitively taxing [22].

Another lifestyle variable that is important when considering cognitive decline is disturbed sleep. Sleep deprivation studies have shown that even short-term sleep deprivation can have deleterious effects on cognition [23]. Moreover, sleep problems, such as insomnia or sleep fragmentation, are associated with an increased risk of future dementia [24–26]. There is also evidence that sleep deprivation is related to accumulation of amyloid-β in the brain [27]. As such, this suggests that the lifestyle variables may interact with biological risk factors for dementia to increase the risk of a neurodegenerative disorder. In addition, individuals with SCD tend to report higher levels of sleep problems [28].

To aid early detection of those who do not have objective cognitive decline, it would seem logical to investigate factors that are known to affect cognition, such as psychological and life-

style factors. While there is evidence that, for example, sleep problems, depression, and stress are associated with cognitive problems and/or future dementia, little is known about whether these variables can be clinically useful in differentiating at an early stage those who have subjective versus objective cognitive decline. The purpose of the present study was to characterize those individuals who turned out to have subjective verbal memory problems, hereafter labeled subjective memory impairment (SMI), from those with objective memory impairment by lifestyle factors that could be easily assessed in early stages of admission to a memory disorders clinic. Verbal memory performance might be particularly important, as a decline in verbal memory tends to be one of the hallmark features of dementia, in particular AD [29, 30]. Moreover, trouble remembering verbal/semantic information tends to be a typical presenting problem among patients at memory disorders clinics. Lifestyle factors that would be of interest include depressive symptoms, sleep, stress, etc.

Furthermore, biomarkers and neuropsychological test performance are also of interest as they contribute information about other aspects of cognition. Early detection of those individuals having high versus low risk factors for cognitive decline in the near future is important. If these individuals are identified early, they can be helped at an early stage with appropriate interventions. It could also potentially save the healthcare system money and resources by not launching a full dementia evaluation prematurely for individuals at low risk of developing a dementing disorder.

Even with early detection as a key interest of the present study, it is also of interest to understand whether lifestyle factors are associated with a combined indicator of cognitive and biological pathology, that is, memory capacity and amyloid-β levels. Specifically, it is of interest to investigate whether there are additional benefits of this combination in terms of being able to differentiate benign subjective complaints from objective decliners.

Materials and Methods

Design and Participants

Only patients who had previously consented to be a part of a database and biobank (GEDOC) for clinical research on neurodegenerative disorders were asked to participate. The sample consisted of consecutive patients presenting to the Memory Disorders Clinic of the Karolinska University Hospital in Stockholm, Sweden, between September 2013 and September 2015. To be evaluated at the clinic, a patient must have been referred by his/her primary care physician; however, a few self-referrals occurred. For the majority of the sample, the reasons for seeking medical attention were complaints of memory problems, either self-reported or noted by a significant other. The inclusion criteria consisted of patients younger than 75 years (range 33–75) with scores between 24 and 30 on the Swedish version of the Mini Mental State Examination (MMSE) [31].

There was no minimum age cut-off. Patients older than 75 years are referred to other types of memory clinics and were therefore unavailable for the present study.

Patients who had previously undergone an evaluation for memory problems or neuropsychological testing were excluded so as to avoid practice effects in the neuropsychological tests and response bias in the questionnaire. All patients were native Swedish speakers and had attended at least primary school in Sweden.

Patients with a diagnosed neurological condition (e.g., Parkinson's disease, Huntington's disease, multiple sclerosis, or amyotrophic lateral sclerosis) were excluded as these conditions often lead to cognitive decline and/or dementia. Moreover, patients with existing diagnoses of psychotic disorders (e.g., schizophrenia, schizoaffective disorder, and bipolar disorder) were excluded, as these disorders are often associated with cognitive problems.

Table 1. Neuropsychological test variables, lifestyle factors, and neurochemical biomarkers

Variable	Value
Age	58.80±8.03
Females	53.1
Education, years	13.80±3.40
IQ (WAIS-IV standard score)	99.17±16.41
RAVLT total learning (*z*-score)	–0.51±1.10
Buschke total learning (*z*-score)	–0.9±1.80
WMS-III Logical Memory I (*z*-score)	0.13±1.30
Much to do (1–5)	3.15±1.12
Control index (1–5)	3.40±0.92
Sleep problems (yes)	58.4
Not rested (1–5)	2.65±1.16
$A\beta_{42}$	857.76±306.78
t-τ	323.63±192.45

Values are presented as means ± SD or percents. IQ, intelligence quotient; WAIS-IV, Wechsler Adult Intelligence Scale – 4th edition; WMS-III, Wechsler Memory Scale, 3rd edition.

Patients with an existing dementia diagnosis were excluded. While it was not an explicit exclusion criterion, none of the patients were diagnosed with a mood disorder, such as major depression, or an anxiety disorder.

A small number of individuals declined to participate (*n* = 23; 11 males and 12 females). These individuals were similar in terms of age (mean = 62.78 years, SD = 9.16) and education (mean = 11.36, SD = 2.97) compared to the final sample. Two of these individuals were excluded from participation based on inability to fill out the questionnaire or other obvious cognitive impairments.

The final sample consisted of 209 individuals (mean age = 58.58, SD = 8.00). Of the final sample, 11 individuals had incomplete data for at least one of the verbal memory tests used to create the clusters (see below). Those individuals were excluded from further analyses. See Table 1 for descriptive data on demographics, test results, questionnaire data, and biological markers.

Procedure and Variables

At the time of neuropsychological data collection, none of the patients had received a diagnosis. Furthermore, the cognitive diagnoses at the clinic are the result of a consensus of neurologist, neuropsychologist, and biomarker data. The SMI and MCI terminology utilized later in this paper refers to the results from memory testing plus neurochemical biomarker data (when available).

All of the patients underwent neuropsychological testing with the standard battery of tests used at the Memory Disorders Clinic of the Karolinska University Hospital. The following tests were included to assess memory (verbal and visual), language, visuoperceptual functions, executive functions, and general intellectual functioning: the Rey Auditory Verbal Learning Test (RAVLT) [32], the Buschke Free and Cued Selective and Reminding Test (FCSRT) [33], Logical Memory I and II (Wechsler Memory Scales, version III) [34], and Wechsler Adult Intelligence Scales-IV [35], select subtests: Information, Similarities, Arithmetic, Matrix Reasoning, Block Design, Digit Span, and Digit Symbol Coding.

As part of the regular protocol at the Karolinska University Hospital Memory Disorders Clinic, all patients who undergo a memory evaluation are asked to give a sample of CSF to check for significant biomarkers for neurodegenerative disease. For those participants who

Table 2. Cluster analysis indicating high versus low scorers on verbal memory retention tests

Variable	Cluster center/standard score	
	n = 121	*n* = 77
RAVLT retention	11/*z* = 0.23	5/*z* =–1.50
Buschke delayed free recall	11/*z* = –0.15	5/*z* = –2.48
WMS-III Logical Memory II	30/*z* = 0.67	12/*z* = –1.0

WMS-III, Wechsler Memory Scale, 3rd edition.

consented (*n* = 170), a CSF sample was collected through a standard lumbar puncture procedure though the L4/L5 intervertebral space. Separate enzyme-linked immunosorbent assays (ELISA) were performed to measure the presence of amyloid-β, p-τ, and t-τ, respectively. The following levels of the biomarkers were considered pathological or abnormal according to guidelines specified by the Clinical Neurochemistry Laboratory at the Sahlgrenska University Hospital: $A\beta_{42}$ <550, p-tau <80 (for individuals aged <50 years, the level is <60), and t-τ >400. In order to make interpretation of the output more straightforward, the values for the biomarkers were divided by 100 and in all of the analyses it is this variable that is depicted.

As part of the regular visit with the neuropsychologist, all of the participants were given a questionnaire of lifestyle questions that were developed specifically for the purpose of this study. The sleep questions were based on the Karolinska Sleep Questionnaire [36]. There was also a general question about the presence of sleep problems (yes/no) pertaining to any phase of adulthood. The questions about current and past memory function were based on standard anamnestic interview items. The questions about negative stress and having much to do, and the 2 questions about control, were constructed specifically for this questionnaire. General background questions such as age, education (number of years), etc. were also included. The following indexes were constructed from the questionnaire items. All indexes had Cronbach's α of 0.6 and above, which is considered an acceptable criterion [37].

The following questionnaire variables were used as potential predictors of memory performance with the following response alternatives unless otherwise indicated (1–5; 1 = disagree completely, 5 = agree completely): perceived past memory functioning (index of 4 variables; Cronbach's α = 0.86), current memory functioning, having much to do, negative stress, control (index of 2 variables: I have good opportunities to control my home and personal life, and I have good opportunities to control my work life; Cronbach's α = 0.66), nonrestorative sleep (index of 3 variables: rarely rested when awakening, need more sleep than I have time for, prefer to take a nap during the daytime; Cronbach's α = 0.63), sleep apnea (index of 2 variables: I snore a great deal, and breathing cessation; Cronbach's α = 0.81) (the 2 sleep indexes were correlated below *r* = 0.18), and depressed (index of 7 variables: I feel hopeful, I do things for others rather than myself, I feel down, I feel happy, I feel lonely, I feel life has been unfair, and I feel my life is meaningful; Cronbach's α = 0.80). For all indexes, averages were computed.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS 24.0) was used for all analyses. A cluster analysis of the retention scores of the verbal memory tests (RAVLT, Buschke, and Logical Memory) was performed in order to characterize delayed memory performance. This resulted in 2 groups, i.e., one with high and one with low retention scores (Table 2). The individuals with low retention scores were at least 1 SD below the mean for each memory test.

Table 3. Demographic and lifestyle factors and biomarkers predicting poor versus good performance groups on verbal memory tests

Variable	Model 1 (n = 158–198)	Model 2 (n =191)	Model 3 (n =191)	Model 4 (n =152)
Gender	0.79 (0.44–1.39)	0.76 (0.41–1.40)	0.59 (0.30–1.19)	0.47 (0.20–1.14)
Age	1.07 (1.03–1.12)	1.07 (1.02–1.11)	1.08 (1.03–1.13)	1.07 (1.01–1.14)
Education	0.85 (0.78–0.94)	0.90 (0.79–0.96)	0.87 (0.79–0.97)	0.89 (0.79–1.00)
Sleep problems	0.37 (0.21–0.67)		0.47 (0.23–0.94)	0.69 (0.30–1.57)
Much to do	0.61 (0.48–0.78)		0.64 (0.49–0.82)	0.64 (0.46–0.89)
Control	1.54 (1.10–2.15)		1.00 (0.70 –1.46)	1.00 (0.64–1.56)
Negative stress	0.72 (0.58 –0.90)		NA[a]	NA[a]
$A\beta_{42/100}$	0.75 (0.66 –0.85)			0.85 (0.74–0.98)
t-$\tau_{/100}$	1.26 (1.06–1.51)			1.28 (0.98–1.69)
Past functioning	0.98 (0.70–1.38)			
Poor memory now	1.11 (0.81–1.54)			
Depressed	0.87 (0.63–1.25)			
Nonrestorative sleep	0.79 (0.61–1.02)			
Snoring/apnea	0.92 (0.72–1.19)			
Past functioning	0.98 (0.70–1.38)			

Values are presented as OR (95% CI). Degrees of freedom in model 1 = 197 (except for $A\beta_{42/100}$ and t-$\tau_{/100}$ for which the degrees of freedom =157), degrees of freedom in model 2 = 190, degrees of freedom for model 3 = 190, and degrees of freedom for model 4 = 151. Only significant variables from model 1 were retained in the other models (except for gender).

The resulting groups were used as the dependent variable in binary logistic regression analyses, with normal memory performance = 0 and poor performance = 1. First, a univariate analysis identifying significant predictors of memory groups was conducted. The significant predictors were then entered into a hierarchical multivariate binary logistic regression analysis. In the hierarchical analysis, model 1 included all variables in a simple regression analysis (Table 3). In model 2, background variables were entered into a multiple regression analysis. In model 3, the lifestyle variables were added. Finally, in model 4, the neurochemical biomarker data were entered.

Results

The univariate logistic regression (Table 3, model 1) showed that an older age, a lower education level, fewer sleep problems, less negative stress, less to do, lower levels of $A\beta_{42}$, and higher levels of t-τ were significantly associated with poor delayed recall performance on the verbal memory tests. Model 2 (overall model score = 24.15, $p < 0.00$) showed significant associations for age ($B = 0.12 \pm 0.03$) and education ($B = -0.03 \pm 0.05$), with an older age predicting low memory scores and more years of education predicting high memory scores. In model 3 (overall model score = 48.28, $p < 0.00$), negative stress was removed because of its high correlation with much to do ($r = 0.81$, $p < 0.001$). Adding much to do ($B = -0.54 \pm 0.17$) and sleep problems ($B = 1.53 \pm 0.44$) as predictors in model 3 resulted in significant OR for both, with high levels predicting high memory performance (Table 3, model 3). Education remained significant, but its effects were attenuated. Model 4 showed that low levels of $A\beta_{42}$ were associated with low memory scores. t-τ did not reach significance. All previously significant variables remained significant except for sleep problems (Table 3, model 4).

In order to further disentangle the high versus low memory performers, a one-way ANOVA was performed with cognitive variables as dependent variables and verbal memory

Table 4. Characterization of normal vs. poor memory performance on cognitive variables

Variable	Normal	Impaired	*F*	*p* value
WAIS-IV Similarities	10.94±3.44	9.76±2.94	6.13	0.00
WAIS-IV Arithmetic	10.89±3.53	8.79±3.11	18.29	0.00
WAIS-IV Matrix Reasoning	10.75±3.20	8.93±3.66	13.73	0.00
WAIS-IV Block Design	10.76±3.16	8.64±2.91	22.50	0.00
WAIS-IV Digit Symbol Coding	9.93±3.04	7.50±2.54	34.19	0.00
WAIS-IV Digit Span	10.54±2.38	8.47±2.67	32.54	0.00
RAVLT total learning	0.56±0.72	–0.88±0.70		
Buschke total learning	0.60±0.65	–0.91±0.80		
WMS-III Logical Memory I	12.13±3.12	8.03±3.17		

Values are presented as means ± SD. WAIS-IV, Wechsler Adult Intelligence Scale, 4th edition; WMS-III, Wechsler Memory Scale, 3rd edition. All means and SD represent scaled scores (mean = 10, SD = 3), except for RAVLT and Buschke, which represent *z*-scores (mean = 0, SD = 1). The last 3 variables were used to create the independent variable, and they were therefore not tested.

cluster as the independent variable (Table 4). The results indicated that the individuals who demonstrated poor memory performance also had a slower information processing speed (WAIS-IV Digit Symbol Coding), lower working memory (WAIS-IV Arithmetic, Digit Span), poorer visuoconstructive skills (WAIS-IV Block Design), and poorer abstract reasoning skills (WAIS-IV Similarities, Matrix Reasoning).

Post hoc Analysis 1

The main results indicated that AB_{42} was a significant predictor of impaired memory performance. Though the purpose of the present study was early detection of SMI, at risk for developing objective cognitive decline, of secondary interest was the question of whether combining memory performance with AB_{42} would help to better characterize individuals with normal or poor memory performance with/without low AB_{42} levels.

Therefore, we carried out a new cluster analysis with an index of the mean retention scores on the verbal memory tests (*z*-transformed) and AB_{42} levels (*z*-transformed). This resulted in two groups, i.e., one with low retention scores and low AB_{42} levels (LL) and one with high retention scores and high AB_{42} levels (HH).

The resulting groups were used as the dependent variable in a binary logistic regression analysis, with normal memory/nonpathological AB_{42} = 0 (n = 112) and poor memory/low AB_{42} = 1 (n = 58). The significant predictors from the main analysis were first used in univariate analyses in order to determine whether they were associated with the new groups. The significant predictors were then entered into a hierarchical multivariate binary logistic regression analysis. Table 5 shows that the predictors from model 1 in the main analysis in Table 3 remained significant and were therefore used in the multivariate analysis. When these were entered, model 3 indicated that individuals who had nonpathological levels of AB_{42} and good memory performance were younger, experienced sleep problems, and reported having a lot to do, significantly more so than those who performed poorly on memory tests and also had low AB_{42} levels.

Post hoc Analysis 2

As there are individuals who perform poorly on memory testing but have nonpathological biomarker levels, we created new groups that also considered AB_{42} levels within memory groups. As such, we used the 2 verbal memory groups and categorized the indi-

Table 5. Results from the binary logistic regression analysis predicting patients with good verbal memory and nonpathological AB_{42} vs. poor verbal memory and pathological AB_{42}

Variable	Model 1 (unadjusted) (n = 166–170)	Model 2 (n =170)	Model 3 (n =164)
Gender	0.75 (0.40–1.42)	0.77 (0.39–1.53)	1.19 (0.48–2.85)
Age	1.13 (1.07–1.19)	1.12 (1.07–1.18)	1.10 (1.04–1.16)
Education	0.93 (0.84–1.02)	0.97 (0.88–1.08)	0.88 (0.78–1.00)
Sleep problems	0.29 (0.15–0.57)		0.25 (0.10–0.58)
Much to do	0.57 (0.43–0.75)		0.64 (0.47–0.88)
Negative stress	0.70 (0.54–0.89)		NA[a]
Control	1.43 (0.99–2.08)		1.07 (0.67–1.72)

Values are presented as OR (95% CI). [a] Variable was removed from model 3 due to a high correlation with "much to do."

viduals in each group into low or high AB_{42}. A less conservative level of 650 was used as the cut-off for AB_{42}, as recommended by the Clinical Neurochemistry Laboratory at the Sahlgrenska University Hospital. This resulted in the following 4 groups: normal verbal memory/high AB_{42} (NH), normal verbal memory/low AB_{42} (NL), impaired verbal memory/high AB_{42} (IH), impaired verbal memory/low AB_{42} (IL). We then conducted a series of two-way ANOVA with verbal memory levels (impaired/normal) representing one factor, levels of AB_{42} (high/low) representing another, and their interaction. The dependent variables were all significant predictors from Table 3, model 1, except AB_{42}.

The ANOVA results showed significant main effects of verbal memory performance for all variables, except control (Table 6). Normal memory performance was associated with a younger age, a higher education level, more sleep problems, more stress, and more negative stress. For AB_{42}, there were significant main effects for age and stress. High AB_{42} was associated with a younger age and higher stress. No interaction effects of verbal memory and AB_{42} were significant.

Discussion

The current study focused on individuals who presented to a memory disorders clinic with a complaint of cognitive decline. The aim was to identify, at an early stage, whether lifestyle factors could differentiate those individuals who would not show objective evidence of memory decline. The results showed that the individuals with no objective decline had more years of education and more sleep problems, and reported having a lot to do in their daily lives, as compared to those with objective memory problems. They also had higher levels of amyloid-β in their CSF, indicating a nonpathological biomarker profile.

Our results on stress in the univariate analysis confirmed the finding of Eckerström et al. [19], showing that negative stress identified the SMI group. This variable, however, was highly correlated with much to do, and it was therefore removed, while "much to do" was retained. With regard to the latter, it seems logical as the probability of memory lapses would be likely to increase with increasing numbers of information units to keep in mind. Having "many things on one's plate" may also a require substantial cognitive effort that takes away resources needed to effectively encode information, leading to a subjective sense of having memory difficulties. To our knowledge, this has not yet been investigated in this patient population and there is a need for replication and more detail in what may be the specific

Table 6. ANOVA results for group differences on lifestyle variables

Variable	NH (n = 78–82)	NL (n = 12)	IH (n = 32–33)	IL (n = 32)	F (memory[c])	F (AB_{42}[c])	F (memory × AB_{42}[c])
Age	56.24±7.05	60.41±9.72	60.08±7.07	64.59±6.82	7.82[b]	9.16[b]	0.01
Education	14.44±3.39	13.92± 4.06	12.67±3.06	13.05±3.11	4.03[a]	0.01	0.47
Sleep problems (yes/no)	65	75	42	44	7.90[b]	0.32	0.18
Much to do (1–5)	4.06±1.00	3.33±1.07	3.55±1.44	2.72±1.30	5.91[a]	11.17[b]	0.04
Negative stress (1–5)	2.94±1.29	3.25±1.60	2.39±1.46	1.91±1.23	12.54[b]	0.11	2.27
Control (1–5)	3.35±0.79	3.54±0.69	3.72±0.95	3.53±1.07	1.09	0.00	1.22

Values are presented as means ± SD or percents. [a] $p < 0.05$. [b] $p < 0.01$. [c] Degrees of freedom = 1/154.

components of "having much to do," including work- and family-related sources of stress. It is worth noting that model 4 in Table 3 showed an increased CI for "having much to do," but this seems to be related to the loss of individuals not wishing to participate in the lumbar puncture.

The finding of sleep problems as a factor that differentiates patients with/without objective memory problems is another new finding; there appear to be no similar previous observations. Rather, sleep problems seem to be a predictor of dementia [38, 39], and they may even play a role in the neurobiological correlates of AD [40].

Surprisingly, in our study, we found that it was the individuals without objective memory problems who reported higher amounts of sleep problems. However, experimental, short-term sleep reduction causes a reduced cognitive ability [23] and even day-to-day variations in sleep quality or sleep duration predict next-day fatigue [41]. We therefore hypothesize that sleep problems every now and then may cause acute cognitive impairment, which may leave the impression of more permanent problems of cognition, which, in turn, may lead to seeking help from primary care units. This hypothesis needs verification, however.

The finding that a higher education level was associated with a lack of objective memory problems is consistent with previous research indicating that individuals with more years of schooling have a reduced risk of developing dementia [42]. As such, education is thought of as a protective factor for cognitive decline [43]. It is possible that those with a higher education level possess a higher cognitive reserve [44] and are therefore able to compensate in the test situation. Another possibility is that there are truly no memory problems in those without objective memory problems in the current study. Instead, it may be their subjective experience of memory decline that is masking the aforementioned lifestyle-related factors. The result that the individuals with no objective memory problem also had intact learning on verbal memory tests provides support for the latter explanation. In other words, there are no other cognitive factors (such as poor attention/working memory) that could better explain why they are experiencing a worsening of memory functions.

Interestingly, there is contradicting evidence that subjective complaints are significant predictors of future cognitive decline. One reason for this could be that the age at the initial examination varies greatly across studies. In the present study, the mean age was 58 years (mean = 58.80, SD = 8.03). Conversely, many studies have included participants with subjective cognitive complaints with a mean age of 70 years or older, which could explain the difference in results [18]. It is likely that the demands of everyday life are quite different for someone in their late 50s as compared to someone well into their 70s. Our finding that "having much to do" was a significant predictor of impaired memory performance could offer some insight into why there is discrepancy in the literature. In other words, younger individuals who seek help for a perceived cognitive decline but do not meet objective criteria may have lifestyle-

related factors that can explain their current functioning, factors other than a preclinical phase of a neurodegenerative disorder. In contrast, it is possible that older individuals with SCD are, in fact, experiencing preclinical stages of dementia.

The significant OR for AB_{42} in model 4 of table 3 suggests that it may contribute to the identification of individuals with SMI, with the latter showing nonpathological levels. Table 4 supports this impression by showing that the combined AB_{42}/memory performance variable is predicted by "having much to do," sleep problems, age, and education. However, the addition of the CSF variables resulted in a sizeable loss of participants, and the results need confirmation in a larger sample. The results from the ANOVA showed that nonpathological levels are independently associated with "having much to do" (and a younger age), but not the other lifestyle variables. This supports the impression that those identified as SMI constitute a cognitively nonpathological group. The ANOVA results also confirm the link between several lifestyle factors and memory performance. The lack of interaction between AB_{42} and memory performance indicates that the two variables do not potentiate each other in the relation with lifestyle factors. In general, it is important to note that the present study could not exclude the possibility that those with normal AB_{42} levels and impaired memory performance had another type of disease process that could explain their memory problems (e.g., vascular dementia and frontotemporal dementia).

Being able to identify individuals who are likely not to have significant memory problems or pathological biomarkers for neurodegenerative disease is highly important. These individuals may not require a full-scale dementia evaluation and may instead be aided by psychological interventions targeting stress and sleep and/or trying to reduce workload/activities during a period of time to determine whether the subjective problems remain. The current study suggests that early screening of important lifestyle factors, such as stress and sleep, in combination with cognitive testing, could be helpful in determining whether to pursue an extended dementia evaluation or not (i.e., brain imaging, lumbar puncture, etc.). As the extended dementia evaluations typically take place in specialized centers (e.g., memory disorder clinics), screening for these factors could perhaps take place in the primary care physician's office and aid in the decision to refer. This could potentially help individuals who are suffering from a subjective sense of cognitive decline by optimizing interventions. For example, receiving targeted psychological interventions (e.g., to alleviate stress and reduce sleep problems) could potentially alleviate lifestyle-related cognitive problems and may be more beneficial than extended medical evaluations. Furthermore, it could save the healthcare system money by not performing unnecessary evaluations and tests on individuals not likely to have an ongoing dementing process.

In the present study, the main focus was on memory impairment as a criterion of objective cognitive decline, mainly because that is a key complaint of those presenting to a memory clinic. In no way do we suggest, however, that only memory testing should replace robust neuropsychological test battery. In fact, the impaired versus normal memory performance groups differed in a number of other cognitive tests, which suggests that memory status also reflects other cognitive measures. As such, this supports the importance of testing across different cognitive domains (as is customary in clinical practice) in order to improve diagnostic accuracy. In fact, a thorough neuropsychological test battery has been shown to improve the reliability and stability of diagnostic workups with MCI patients [45].

The present study has several limitations. One concern is the loss of data on potential pathological biomarkers due to the number of patients (n = 40) who did not undergo lumbar puncture. Therefore, we do not know if there is some form of selection bias in the group of individuals who chose not to provide CSF for analysis. Another limitation is the lifestyle questionnaire, which – to a large extent – included nonvalidated items as well as limited response alternatives for some domains. For instance, the yes/no response alternative for the sleep

item prevented a more nuanced analysis of the role of sleep. A similar study should be carried out with a wider range of response alternatives.

One could consider the use of established scales for stress and sleep. Moreover, inclusion of objective sleep measures would have been desirable. A strength of this study is the use of three memory tests for differentiation of SMI from amnestic MCI. Furthermore, clinically relevant questions targeting the issues commonly reported in memory disorder clinics have been utilized systematically.

An unexpected finding was that depressive symptoms failed to significantly differentiate between the subjective complaints and cases of objective decline. It is possible that depressive symptoms constitute a common problem for all patients presenting to memory disorder clinics and that it is therefore not useful to characterize memory performance in these individuals.

Conclusion

The present study suggests that lifestyle-related factors such as "having much to do" and experiencing disturbed sleep are useful for gaining a better understanding of referred patients who do not show objective impairment on neuropsychological testing. These results offer interesting insights into the possible underlying reasons why individuals initially seek help for subjective cognitive problems. This insight may also be used at early screening to identify individuals who might be helped through psychoeducation and treatment of stress reactions and disturbed sleep.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

1 American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington (DC): American Psychiatric Association; 2013.
2 Prince MW, Guerchet M, Ali GC, Wu Y, Prina AM. World Alzheimer Report 2015: the lobal impact of dementia – an analysis of prevalence, incidence, costs and trends. London: ALZ; 2015
3 Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010 Jan;9(1):119–28.
4 Perrin RJ, Fagan AM, Holtzman DM. Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. Nature. 2009 Oct;461(7266):916–22.
5 Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013 Feb;12(2):207–16.
6 van Harten AC, Visser PJ, Pijnenburg YA, Teunissen CE, Blankenstein MA, Scheltens P, et al. Cerebrospinal fluid Aβ42 is the best predictor of clinical progression in patients with subjective complaints. Alzheimers Dement. 2013 Sep;9(5):481–7.
7 Alzheimer Sverige [Internet]. Utbredning och statistik kring minnessjukdomar. [cited 2018 Aug 31]. Available from: http://alzheimersverige.se/fakta-forskning/utbredning-och-statistik/.
8 Wimo A, Jönsson L, Fratiglioni L, Sandman PO, Gustavsson A, Sköldunger A, et al. The societal costs of dementia in Sweden 2012 – relevance and methodological challenges in valuing informal care. Alzheimers Res Ther. 2016 Nov;8(1):59.
9 Garcia-Ptacek S, Cavallin L, Kåreholt I, Kramberger MG, Winblad B, Jelic V, et al. Subjective cognitive impairment subjects in our clinical practice. Dement Geriatr Cogn Disord Extra. 2014 Nov;4(3):419–30.
10 Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chételat G, et al.; Subjective Cognitive Decline Initiative (SCD-I) Working Group. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement. 2014 Nov;10(6):844–52.

11 Rönnlund M, Sundström A, Adolfsson R, Nilsson LG. Subjective memory impairment in older adults predicts future dementia independent of baseline memory performance: evidence from the Betula prospective cohort study. Alzheimers Dement. 2015 Nov;11(11):1385–92.
12 Reisberg B, Shulman MB, Torossian C, Leng L, Zhu W. Outcome over seven years of healthy adults with and without subjective cognitive impairment. Alzheimers Dement. 2010 Jan;6(1):11–24.
13 Hessen E, Eckerström M, Nordlund A, Selseth Almdahl I, Stålhammar J, Bjerke M, et al. Subjective Cognitive Impairment Is a Predominantly Benign Condition in Memory Clinic Patients Followed for 6 Years: the Gothenburg-Oslo MCI Study. Dement Geriatr Cogn Disord Extra. 2017 Feb;7(1):1–14.
14 Lehrner J, Coutinho G, Mattos P, Moser D, Pflüger M, Gleiss A, et al. Semantic memory and depressive symptoms in patients with subjective cognitive decline, mild cognitive impairment, and Alzheimer's disease. Int Psychogeriatr. 2017 Jul;29(7):1123–35.
15 Rizk-Jackson A, Insel P, Petersen R, Aisen P, Jack C, Weiner M. Early indications of future cognitive decline: stable versus declining controls. PLoS One. 2013 Sep;8(9):e74062.
16 Fernández-Blázquez MA, Ávila-Villanueva M, Maestú F, Medina M. Specific Features of Subjective Cognitive Decline Predict Faster Conversion to Mild Cognitive Impairment. J Alzheimers Dis. 2016 Mar;52(1):271–81.
17 Kielb S, Rogalski E, Weintraub S, Rademaker A. Objective features of subjective cognitive decline in a United States national database. Alzheimers Dement. 2017 Dec;13(12):1337–44.
18 Hessen E, Nordlund A, Stålhammar J, Eckerström M, Bjerke M, Eckerström C, et al. T-Tau is Associated with Objective Memory Decline Over Two Years in Persons Seeking Help for Subjective Cognitive Decline: A Report from the Gothenburg-Oslo MCI Study. J Alzheimers Dis. 2015;47(3):619–28.
19 Eckerström M, Berg AI, Nordlund A, Rolstad S, Sacuiu S, Wallin A. High Prevalence of Stress and Low Prevalence of Alzheimer Disease CSF Biomarkers in a Clinical Sample with Subjective Cognitive Impairment. Dement Geriatr Cogn Disord. 2016;42(1-2):93–105.
20 Hollands S, Lim YY, Buckley R, Pietrzak RH, Snyder PJ, Ames D, et al. Amyloid-β related memory decline is not associated with subjective or informant rated cognitive impairment in healthy adults. J Alzheimers Dis. 2015;43(2):677–86.
21 Singh-Manoux A, Dugravot A, Ankri J, Nabi H, Berr C, Goldberg M, et al. Subjective cognitive complaints and mortality: does the type of complaint matter? J Psychiatr Res. 2014 Jan;48(1):73–8.
22 Zuniga KE, Mackenzie MJ, Kramer A, McAuley E. Subjective memory impairment and well-being in community-dwelling older adults. Psychogeriatrics. 2016 Jan;16(1):20–6.
23 Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep. 2003 Mar;26(2):117–26.
24 Lim AS, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep Fragmentation and the Risk of Incident Alzheimer's Disease and Cognitive Decline in Older Persons. Sleep (Basel). 2013 Jul;36(7):1027–32.
25 Osorio RS, Pirraglia E, Agüera-Ortiz LF, During EH, Sacks H, Ayappa I, et al. Greater risk of Alzheimer's disease in older adults with insomnia. J Am Geriatr Soc. 2011 Mar;59(3):559–62.
26 Bokenberger K, Ström P, Dahl Aslan AK, Johansson AL, Gatz M, Pedersen NL, et al. Association Between Sleep Characteristics and Incident Dementia Accounting for Baseline Cognitive Status: A Prospective Population-Based Study. J Gerontol A Biol Sci Med Sci. 2017 Jan;72(1):134–9.
27 Ooms S, Overeem S, Besse K, Rikkert MO, Verbeek M, Claassen JA. Effect of 1 night of total sleep deprivation on cerebrospinal fluid β-amyloid 42 in healthy middle-aged men: a randomized clinical trial. JAMA Neurol. 2014 Aug;71(8):971–7.
28 Cavuoto MG, Ong B, Pike KE, Nicholas CL, Bei B, Kinsella GJ. Better Objective Sleep Quality in Older Adults with High Subjective Memory Decline. J Alzheimers Dis. 2016 Jun;53(3):943–53.
29 Andersson C, Lindau M, Almkvist O, Engfeldt P, Johansson SE, Eriksdotter Jonhagen M. Identifying patients at high and low risk of cognitive decline using Rey Auditory Verbal Learning Test among middle-aged memory clinic outpatients. Dement Geriatr Cogn Disord. 2006;21(4):251–9.
30 Estévez-González A, Kulisevsky J, Boltes A, Otermín P, García-Sánchez C. Rey verbal learning test is a useful tool for differential diagnosis in the preclinical phase of Alzheimer's disease: comparison with mild cognitive impairment and normal aging. Int J Geriatr Psychiatry. 2003 Nov;18(11):1021–8.
31 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189–98.
32 Schmidt M. Rey Auditory Verbal Learning Test - a handbook. Los Angeles: Western Psychological Services; 1996.
33 Buschke H. Cued recall in amnesia. J Clin Neuropsychol. 1984 Nov;6(4):433–40.
34 Wechsler D. Wechsler Memory Scale - (WMS-III) administration and scoring manual, Third. San Antonio (TX): The Psychological Corporation; 1997b.
35 Wechsler D. Wechsler Adult Intelligence Scale - (WAIS-IV), Fourth. San Antonio (TX): Pearson; 2008.
36 Akerstedt T, Ingre M, Broman JE, Kecklund G. Disturbed sleep in shift workers, day workers, and insomniacs. Chronobiol Int. 2008 Apr;25(2):333–48.
37 Cronbach LJ. Coefficient alpha and the internal structure of tests. Psychometrika. 1951;16(3):297–334.
38 Tsapanou A, Gu Y, Manly J, Schupf N, Tang MX, Zimmerman M, et al. Daytime Sleepiness and Sleep Inadequacy as Risk Factors for Dementia. Dement Geriatr Cogn Disord Extra. 2015 Jul;5(2):286–95.

39 Hahn EA, Wang HX, Andel R, Fratiglioni L. A change in sleep pattern may predict Alzheimer disease. Am J Geriatr Psychiatry. 2014 Nov;22(11):1262–71.
40 Lucey BP, Bateman RJ. Amyloid-β diurnal pattern: possible role of sleep in Alzheimer's disease pathogenesis. Neurobiol Aging. 2014 Sep;35 Suppl 2:S29–34.
41 Akerstedt T, Axelsson J, Lekander M, Orsini N, Kecklund G. Do sleep, stress, and illness explain daily variations in fatigue? A prospective study. J Psychosom Res. 2014 Apr;76(4):280–5.
42 Brayne C, Ince PG, Keage HA, McKeith IG, Matthews FE, Polvikoski T, et al.; EClipSE Collaborative Members. Education, the brain and dementia: neuroprotection or compensation? Brain. 2010 Aug;133(Pt 8):2210–6.
43 Sharp ES, Gatz M. Relationship between education and dementia: an updated systematic review. Alzheimer Dis Assoc Disord. 2011 Oct-Dec;25(4):289–304.
44 Vaqué-Alcázar L, Sala-Llonch R, Valls-Pedret C, Vidal-Piñeiro D, Fernández-Cabello S, Bargalló N, et al. Differential age-related gray and white matter impact mediates educational influence on elders' cognition. Brain Imaging Behav. 2017 Apr;11(2):318–32.
45 Bondi MW, Smith GE. Mild cognitive impairment: a concept and diagnostic entity in need of input from neuropsychology. J Int Neuropsychol Soc. 2014 Feb;20(2):129–34.