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Amyloid Plaques and Symptoms of Depression Links to Medical Help-Seeking due to Subjective Cognitive Decline

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Abstract.
Background: Subjective cognitive decline (SCD) is associated with an increased risk of Alzheimer's disease (AD). However, patients reporting SCD to their general practitioner are not always referred to a memory clinic.
Objective: To investigate whether prior history of medical help-seeking is associated with AD biomarker abnormality, worse cognitive performance, and/or depressive symptoms in SCD.
Methods: We compared levels of cerebrospinal fluid (CSF) $A\beta_{1\text{-}42}$, cognitive performance, and depressive symptoms (15-item Geriatric Depression Scale, GDS-15) between healthy controls ($n=88$), SCD with a history of medical help seeking (SCD-HS, $n=67$), and SCD non help-seekers (SCD-NHS, $n=44$). Cases with evidence of amyloid plaques (CSF $A\beta_{1\text{-}42}$ $\leq$708 ng/l) and symptoms of depression (GDS-15$\geq$6) were determined in both SCD groups.
Results: The SCD-HS group had lower CSF $A\beta_{1\text{-}42}$ ($p<0.01$), lower word list learning and memory recall ($p<0.0001$), and an increased level of depressive symptoms ($p<0.0001$) compared to controls and SCD-NHS cases. The SCD-HS group had more cases with symptoms of depression ($n=12$, 18%) and amyloid plaques ($n=18$, 27%) compared to SCD-NHS ($n=1$, 2% and $n=7$, 16%, respectively). None of the SCD-HS cases and only one SCD-NHS case had concurrent symptoms of depression and amyloid plaques. The SCD-HS cases showed equal word list learning and memory performance regardless of amyloid status or symptoms of depression.
Conclusion: Medical help-seeking in SCD is associated with an increased risk of AD pathology or symptoms of depression. However, subtle memory deficits are seen in SCD help-seekers, also without amyloid plaques or symptoms of depression.

Keywords: Alzheimer's disease, amyloid plaques, cerebrospinal fluid $A\beta_{1\text{-}42}$, cognitive symptoms, early diagnosis, help-seeking behavior, medical help-seeking, neuropsychiatric symptoms, neuropsychological tests, subjective cognitive decline

INTRODUCTION

Studies have shown that the pathophysiological underpinnings of Alzheimer's disease (AD) may begin 10 to 15 years before the emergence of detectable mild cognitive impairment (MCI) [1, 2].

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This extended preclinical phase constitutes a possible window for preventive interventions [1, 3]. Improved methods for earlier identification of AD in the preclinical phase are therefore needed. Subjective cognitive decline (SCD), the self-perceived decline in cognitive functions while performing within the normal range on cognitive tests, is associated with an increased risk of MCI and dementia due to AD [4–10]. Indeed, the presence of amyloid plaques, a hallmark of AD, in cognitively healthy persons with SCD has shown to predict later decline in memory functions [11–13]. Moreover, SCD may be accompanied by functional alterations in hippocampal integrity reflecting compensatory mechanisms that preserve memory performance [14].

However, SCD is heterogeneous, often a benign condition, and most cases do not progress to dementia [4, 5, 15–19]. A recent study found increased levels of stress/depressive symptoms in SCD with a low prevalence of altered CSF AD biomarkers over time, suggesting that AD is not the most frequent etiology [15]. At present, AD is assessed using cerebrospinal fluid (CSF) or positron emission tomography (PET) imaging analyses, procedures which are invasive or costly. Thus, methods to improve the detection of SCD cases with incipient AD are of value for the selection of candidates eligible for early intervention trials.

Recruitment of MCI and SCD participants through memory clinics include individuals with higher rates of abnormal CSF biomarkers and increased brain amyloid-β (Aβ) deposition as compared to self-referred participants from the community [20–23]. We and others have shown that MCI recruited through memory clinics also have poorer cognitive function than community samples [21, 24, 25]. However, while memory clinic SCD cases have shown higher conversion rates to MCI compared to community cases [23, 26], and lower baseline cognitive performance in one study [27], most studies have not found any baseline cognitive differences in SCD cases due to recruitment source bias [22, 24, 26]. The biases observed from recruiting memory clinic SCD cases may stem from worries or concerns felt by either patients, or their families reaching a threshold prompting the person to seek medical help. Indeed, worried individuals with SCD have increased risk of developing objective cognitive decline [6, 28, 29]. However, patients who report SCD to their general practitioner (GP) may not be referred to a memory clinic for assessment [30]. In a previous study, we found no significant cognitive differences between SCD cases recruited from memory clinics as compared to SCD cases recruited from a community sample [24].

In the present study, we hypothesize that SCD cases with a history of medical help-seeking, independent of recruitment source, carry a higher risk of AD compared to non-help-seeking SCD cases and healthy controls. We compare levels of CSF AD biomarkers ($A\beta_{1\text{-}42}$, total tau, and phosphorylated tau) and cognitive performance between these groups. In addition, we investigate levels of depressive symptoms between groups, as depressive symptoms may play a role in the expression of SCD as well as medical help-seeking. Lastly, we investigate the association between pathological CSF $A\beta_{1\text{-}42}$ levels (e.g., the presence of amyloid plaques) and frequencies of cases with symptoms of depression (15-item Geriatric Depression Scale (GDS-15)$\geq$6) [31], in both help-seeking and non-help-seeking SCD cases.

METHODS

The present study is part of the Norwegian multicenter study, Dementia Disease Initiation (DDI), a collaboration between all Norwegian health regions and University hospitals. Between January 2013 and January 2019, participants with self-reported cognitive decline and healthy controls were recruited. The DDI cohort comprises self-referred participants following advertisements in media, newspapers, or news bulletins, and patients referred from their general practitioners to local memory clinics. Healthy controls were included from spouses of patients with dementia/cognitive disorder, and from patients who completed lumbar puncture for orthopedic surgery. Classification of participants as either healthy controls, SCD, MCI, or dementia were performed according to published criteria [28, 32–34].

Inclusion criteria were a native language of Norwegian, Swedish, or Danish and age between 40 and 80 years. Participants with a medical history of brain trauma or brain disorder, including clinical stroke, dementia, severe psychiatric disorder, severe somatic disease that might influence cognitive functions, or intellectual disability or other developmental disorders were excluded. All participants were examined with a case report form developed for DDI. The case report form is administrated as a structured interview and includes a standardized assessment protocol for cognitive impairment and SCD (see below), medical history from participant and informant, physical

and neurological examinations as well as the 15-item version of the GDS [31]. All participants underwent cognitive examination comprising the Mini-Mental State Examination (MMSE-NR) [35], non-verbal cognitive screening (The clock drawing test) [36], verbal memory (CERAD word list) [37], visuoperceptual ability (VOSP silhouettes) [38], psychomotor speed and executive functions (Trail making (TMT) A and B) [39], and word fluency (COWAT) [40]. For further description of the DDI cohort and methods, see Fladby et al. (2017) [20].

Classification of SCD and cognitively normal healthy controls

Classification of subjects as either SCD or cognitively normal healthy controls was performed as part of a structured interview with standardized questions, the DDI case report form. It includes a broad description of participants' symptoms and experience of subjective cognitive decline according to the suggested framework by the working group of SCD-I. It considers onset of decline, cognitive domain, patient concerns and worries, if feeling of being worse compared to age-matched peers is present, and when available, informant confirmation of decline. Participants recruited from other sources than the memory clinics were asked if they had previously sought medical help due to SCD. Published norms (adjusted for age, sex, and educational effects) for the different tests were used to classify performance as normal or abnormal [38, 41, 42]. We applied a threshold of GDS-15 total score $\geq$6 [31] for symptom of depression [31]. Cognitive performance was deemed normal if the participant obtained normative scores above T = 35 ($\geq$1.5 SD) on either CERAD word list (delayed recall), VOSP silhouettes, TMT-B, or COWAT. Participants with normal cognitive performance on standardized cognitive tests in combination with subjective decline in any cognitive domain were classified as SCD according to the SCD-I framework, which requires self-experienced cognitive decline unrelated to an acute event in any cognitive domain, normal functions of daily living (ADL-function), and performance within the normal range on standardized cognitive tests [28]. In contrast, cases classified as healthy controls had not experienced cognitive decline. For the purpose of this study, SCD participants were further classified as medical help-seekers (HS, $n = 67$) or non-help-seekers (NHS, $n = 44$). Participants recruited from GP referral were automatically classified as HS ($n = 46/67$, 69%). In addition, participants recruited from advertisement who answered yes to having a prior history of seeking help for SCD were also classified as HS ($n = 21/67$, 31%). Participants recruited from advertisement who had not sought help for SCD were classified as NHS ($n = 44$).

Participants

The DDI cohort comprises cases classified as healthy controls, SCD, MCI, or dementia ($n = 658$). For the present study, only cognitively normal healthy controls and SCD cases with available CSF AD biomarkers from the DDI cohort ($n = 199$) were included. Our sample comprised cognitively normal healthy controls ($n = 88$), SCD-HS ($n = 67$), and SCD-NHS ($n = 44$). Informant confirmation of SCD was only available for a small subset of SCD cases ($n = 39/111$, 35%), thus no statistical analyses were performed using this variable. However, type of SCD complaint (memory, language, orientation, or attention/executive functions) was included in our between-group analyses. An outline of the participant inclusion process is depicted in Fig. 1. For description of group demographics, see Table 1.

CSF collection and handling

Following DDI procedures as described previously [20], lumbar puncture was performed before noon, CSF was collected in polypropylene tubes (Thermo Nunc) and centrifuged within 4 h at 2000 g for 10 min at room temperature. The supernatant was transferred to new tubes and frozen at –80°C prior to analysis. All CSF samples were analyzed at the Department of Interdisciplinary Laboratory Medicine and Medical Biochemistry at Akershus University Hospital, and samples from other DDI sites were frozen before shipment to the laboratory. Handling and analysis followed the BIOMARKAPD SOPs [43]. Analyses were performed consecutively as part of routine work-up, as described previously [20, 44], and showed an optimal cut-off at CSF $A\beta_{1-42}$ $\leq$708 for amyloid plaque pathology as compared to a PET [18F]-flutemetamol uptake study [44].

Protein biomarker measurements

Commercial enzyme-linked immunosorbent assays based on monoclonal antibodies were used to measure CSF levels of the following protein biomarkers: $A\beta_{1-42}$, t-tau, and p-tau were deter-

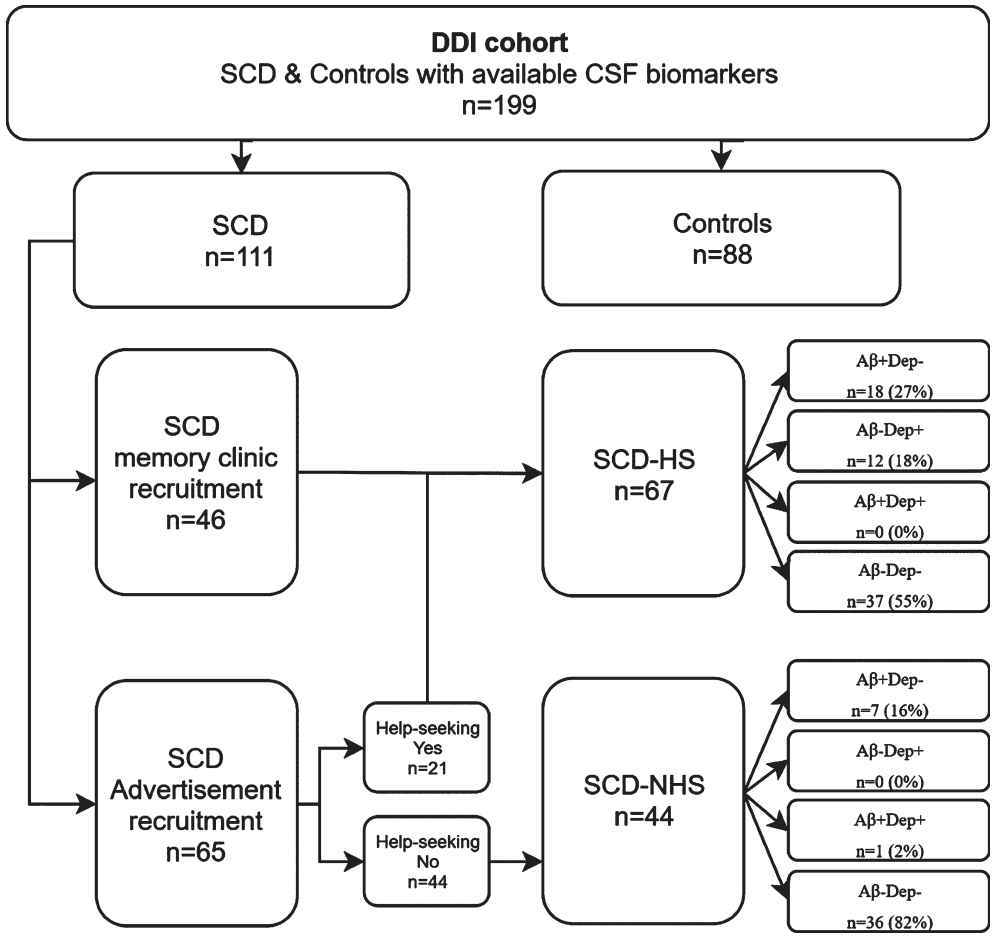

Fig. 1. A total of $n = 199$ subjective cognitive decline (SCD) and controls from the Dementia Disease Initiation (DDI) cohort comprising $n = 88$ cognitively healthy controls, $n = 67$ SCD with a history of medical help seeking (SCD-HS) and $n = 44$ SCD non-help-seekers (SCD-NHS) were included.

mined using Innotest Aβ (1–42), Innotest h-Tau Ag, and Innotest Phospho-Tau (181P) (Fujirebio, Ghent, Belgium), respectively.

Statistical analysis

Examination of QQ-plots, histograms, and the Shapiro-Wilks test of normality were used to assess normality. For variables with normal distributions, assessment of between group differences in CSF biomarker levels, cognition, age, and years of education were performed using one-way ANOVAs with planned comparisons. Kruskal-Wallis test with Dunn's non-parametric pairwise *post-hoc* test was used to assess group differences in variables with non-normal distributions (CSF $A\beta_{1\text{-}42}$, CSF t-tau, CSF t-tau, and MMSE). The dichotomous variable "sex" and between-group distributions of SCD complaint type were assessed using a chi square test. For statistically significant between-group differences using one-way ANOVAs or Kruskal-Wallis tests, effect sizes (eta squared, η^2) are reported. Groups were compared in the following manner: First, we compared healthy controls to both the SCD-HS and SCD-NHS groups. Then, SCD-HS group was compared to SCD-NHS group. Lastly, we compared the distribution of symptoms of depression with or without the presence of amyloid plaques between the SCD-HS and SCD-NHS groups using a chi square test as well as observed numbers and percentages. This yielded four groups comprising cases with amyloid plaques without symptoms of depression (Aβ+Dep-), symptoms of depression without amyloid plaques (Aβ-Dep+), amyloid plaques and symptoms of depression (Aβ+Dep+), and lastly, cases with neither amyloid plaques nor symptoms of

Table 1
Between-group comparisons of CSF biomarkers, cognitive performance, demographics and depressive symptoms

Variable	Groups			F / χ^2 / η^2 / (p)	ANOVA planned contrasts (p)		
	1. Controls $n=88$	2. SCD-HS $n=67$	3. SCD-NHS $n=44$		1 versus 2	1 versus 3	2 versus 3
Age							
Mean (SD)	61.4 (9.4)	60.8 (8.3)	64.2 (9.9)	$F=1.9$, (n.s)	*n.s*	*n.s*	*n.s*
Female							
n (%)	48 (55%)	33 (49%)	17 (39%)	$\chi^2=2.8$, (n.s)	*	*	*
Years of education							
Mean (SD)	14.0 (3.3)	13.6 (3.3)	13.5 (3.3)	$F=0.6$, (n.s)	*	*	*
GDS 15							
Mean (SD)	0.7 (1.1)	3.9 (3.0)	1.7 (2.0)	$F=43.6$, $\eta^2=0.31$, **(<0.0001)**	**<0.0001**	**<0.05**	**<0.0001**
MMSE							
Median (IQR)	30 (1)	29 (1)	30 (2)	$\chi^2=0.3$, (n.s)	*	*	*
CERAD Learning T-score							
Mean (SD)	52.9 (9.8)	47.0 (9.6)	53.4 (9.0)	$F=8.8$, $\eta^2=0.08$, **(<0.0001)**	**<0.0001**	*n.s*	**<0.001**
CERAD Recall T-score							
Mean (SD)	52.8 (7.8)	47.6 (8.9)	52.8 (9.0)	$F=8.3$, $\eta^2=0.08$, **(<0.001)**	**<0.0001**	*n.s*	**<0.01**
TMT-A T-score							
Mean (SD)	49.4 (9.0)	49.9 (8.4)	47.5 (9.7)	$F=1.1$, (n.s)	*	*	*
TMT-B T-score							
Mean (SD)	52.2 (7.6)	50.5 (8.7)	50.8 (7.8)	$F=1.0$, (n.s)	*	*	*
COWAT T-score							
Mean (SD)	51.7 (8.2)	51.8 (9.3)	51.9 (8.9)	$F=1.0$, (n.s)	*	*	*
VOSP silhouettes							
Mean (SD)	52.6 (9.0)	51.1 (11.0)	54.9 (9.7)	$F=0.2$, (n.s)	*	*	*
CSF Aβ1-42							
Mean (SD)	1055 (230)	932 (310)	1022 (296)	$F=3.9$, $\eta^2=0.04$, **(<0.05)**	**<0.01**	*n.s*	*n.s*
CSF t-tau							
Mean (SD)	324 (152)	335 (210)	364 (181)	$F=0.7$, (n.s)	*n.s*	*n.s*	*n.s*
CSF p-tau							
Mean (SD)	53 (19)	57 (30)	59 (23)	$F=1.0$, (n.s)	*n.s*	*n.s*	*n.s*
SCD Memory *n* (%)		53 (84%)	32 (80%)	$\chi^2=0.6$, (n.s)	*	*	*
SCD Executive functions *n* (%)		3 (5%)	3 (7%)	$\chi^2=0.3$, (n.s)	*	*	*
SCD Language *n* (%)		5 (8%)	10 (13%)	$\chi^2=0.5$, (n.s)	*	*	*
SCD Orientation *n* (%)		2 (3%)	0 (0%)	$\chi^2=1.3$, (n.s)	*	*	*

n, sample size; n.s., non-significant results; *No contrasts/*post hoc* tests performed; F, F-statistic; χ^2, chi-square or Kruskal-Wallis statistic; η^2, eta-squared, p, p-value.

depression (Aβ-Dep-). All analyses were performed in the Statistical Package for Social Sciences (SPSS) version 25.

Ethics

The Regional Medical Research Ethics committee approved the study. All participants gave their written informed consent before taking part in the study. All further study conduct was in line with the guidelines provided by the Helsinki declaration of 1964; revised 2013 and the Norwegian Health and Research act.

RESULTS

Group comparisons of cognitive performance and demographics

Between-group comparisons of cognitive variables and demographics are shown in Table 1. While the SCD-NHS group had similar cognitive scores as the healthy controls, SCD-HS had significantly lower scores on both CERAD learning and delayed memory recall as compared to both controls ($p<0.0001$; $p<0.0001$) and SCD-NHS group ($p<0.0001$; $p<0.001$). There was no significant difference in type of SCD cognitive complaint, age, years of education, or sex distribution between the groups.

Group comparisons of GDS-15 depressive symptoms

Between-group comparisons of GDS-15 are shown in Table 1.

Both SCD-HS ($p<0001$) and SCD-NHS (<0.05) groups reported higher levels of depressive symptoms as compared to controls. However, SCD-HS group reported more depressive symptoms than the SCD-NHS group ($p<0.0001$).

Between-group CSF AD biomarkers comparisons

Between-group comparisons of CSF variables are shown in Table 1.

While SCD-NHS had similar CSF $A\beta_{1\text{-}42}$ levels as compared to controls, SCD-HS had lower CSF $A\beta_{1\text{-}42}$ as compared to both SCD-NHS ($p < 0.05$) and controls ($p < 0.001$).

We found no between-group differences in CSF t-tau or p-tau levels.

Within-group distributions of amyloid plaques and symptoms of depression

There were higher rates of Aβ+Dep- cases ($n = 18$, 27%) within the SCD-HS group as compared to the SCD-NHS group (Aβ+Dep-, $n = 7$, 16%, $p < 0.0001$). Moreover, we found higher rates of Aβ-Dep+ cases ($n = 12$, 18%, $p < 0.0001$) in the SCD-HS group as compared to no cases within the SCD-NHS group. No Aβ+Dep+ cases were found in the SCD-HS group and only one case within the SCD-NHS group was Aβ+Dep+ (see Table 2).

Within-group differences in cognitive performance and demographics

In light of the results shown in the previous section, we performed Kruskal-Wallis tests with Bonferroni adjusted Dunn's pairwise comparisons to investigate potential differences in cognitive performance and demographics between SCD help-seekers with either amyloid plaques or symptoms of depression and cases with neither symptoms of depression nor amyloid plaques (see Table 3). While help-seekers with symptoms of depression were younger (M = 55.8, SD = 8.4) compared to cases with amyloid plaques (M = 64.5, SD = 8.3, $p < 0.05$), no significant between-group differences in cognitive performance or demographics were found.

Table 2
Frequencies of amyloid plaques and symptoms of depression in SCD-HS and SCD-NHS

Groups	SCD-HS n (%)	SCD-NHS n (%)	χ^2 (p)
Aβ- Dep-	37 (55%)	36 (82%)	$\chi^2 = 73.0$, **p < 0.0001**
Aβ+ Dep-	18 (27%)	7 (16%)	$\chi^2 = 25.0$, **p < 0.0001**
Aβ- Dep+	12 (18%)	0 (0%)	*
Aβ+ Dep+	0 (0%)	1 (2%)	*

p, *p*-value; n, sample size; χ^2, chi-square test; Aβ+/–, presence or absence of amyloid plaque pathology (CSF $A\beta_{1\text{-}42} \geq 708$); Dep+/–, presence or absence of symptoms of depression (GDS ≥ 6). *No statistical tests performed.

DISCUSSION

The main finding of this study was that SCD cases with self-reported history of medical help-seeking had lower levels of CSF $A\beta_{1\text{-}42}$, weaker performance on the CERAD word list memory test, and increased levels of depressive symptoms compared to both SCD non-help-seekers and controls. However, additional analyses revealed that the SCD help-seeker group comprised three subgroups: 1) subjects with symptoms of depression, 2) subjects with amyloid plaques, and 3) subjects with neither amyloid plaques nor symptoms of depression. Of note, none of the SCD help-seekers had both amyloid plaques and symptoms of depression. Interestingly, all three subgroups of SCD help-seekers showed equal memory performance, regardless of amyloid status or symptoms of depression.

While many studies have found recruitment source differences in both AD biomarker prevalence and cognitive performance in MCI [21, 24, 25], studies on SCD have been inconsistent [22, 24, 26, 27]. A recent meta-analysis found no difference in the risk of progression of SCD patients recruited by different means [4]. This is in line with a previous report from our group, showing no significant differences in cognitive performance or demographics between memory-clinic referred and self-referred SCD cases from the community [24]. Inconsistencies between studies may partly be due to help-seeking SCD patients not being referred for extensive assessment at memory clinics by their GP. These individuals may subsequently volunteer for research participation.

Several studies have shown that SCD cases recruited through memory clinics show increased rates of pathological AD biomarkers [20, 26, 27]. In the present study, we found lower CSF $A\beta_{1\text{-}42}$ in the SCD-HS group as compared to both SCD-NHS and controls. Additional analyses confirmed that the SCD-HS group had a higher rate of amyloid plaques ($n = 18$, 27%) compared to the SCD-NHS group ($n = 8$, 18%). The majority of these cases ($n = 46$, 69%) were indeed recruited from memory clinics, which supports the idea of a recruitment bias when including at-risk cases from memory clinics [23, 26, 27]. Moreover, we also found subtle deficits in memory performance in the SCD-HS group compared to both SCD-NHS and controls. This is in contrast to our previous study where no differences in cognitive performance between memory-clinic referred and self-referred SCD cases from the community

Table 3
Comparisons of demographics and cognitive performance between SCD help-seekers with either amyloid plaques or symptoms of depression and cases with neither amyloid plaques nor symptoms of depression

Variable	Groups			χ^2 / η^2 / (*p*)	Bonferroni adjusted Dunn's pairwise comparisons (*p*)		
	1. SCD-HS Aβ-Dep- *n* = 37	2. SCD-HS Aβ+Dep- *n* = 18	3. SCD-HS Aβ-Dep+ *n* = 12		1 versus 2	1 versus 3	2 versus 3
Age							
Mean (SD)	60.7 (7.6)	64.5 (8.3)	55.8 (8.4)	$\chi^2 = 7.7$, $\eta^2 = 0.09$, **(<0.05)**	*n.s*	*n.s*	**<0.05**
Female							
n (%)	21 (57%)	8 (44%)	4 (33%)	$\chi^2 = 2.2$, (n.s)	*	*	*
Years of education							
Mean (SD)	13.8 (3.5)	13.5 (3.2)	12.8 (2.9)	$\chi^2 = 0.5$, (n.s)	*	*	*
MMSE							
Median (IQR)	29 (2)	30 (2)	29 (3)	$\chi^2 = 0.4$, (n.s)	*	*	*
CERAD Learning T-score							
Mean (SD)	47.4 (10.2)	48.8 (8.7)	43.2 (8.6)	$\chi^2 = 3.4$, (n.s)	*	*	*
CERAD Recall T-score							
Mean (SD)	47.8 (9.2)	47.4 (9.3)	47.1 (7.5)	$\chi^2 = 0.9$, (n.s)	*	*	*
TMT-A T-score							
Mean (SD)	48.9 (8.3)	58.9 (8.8)	48.5 (7.5)	$\chi^2 = 2.4$, (n.s)	*	*	*
TMT-B T-score							
Mean (SD)	51.9 (9.4)	50.7 (6.7)	45.9 (7.8)	$\chi^2 = 3.3$, (n.s)	*	*	*
COWAT T-score							
Mean (SD)	52.4 (8.8)	51.2 (10.1)	51.0 (10.5)	$\chi^2 = 0.2$, (n.s)	*	*	*
VOSP silhouettes							
Mean (SD)	51.5 (13.0)	51.4 (8.1)	59.8 (9.2)	$\chi^2 = 0.9$, (n.s)	*	*	*

Aβ+/–, presence or absence of amyloid plaque pathology (CSF $A\beta_{1\text{-}42} \leq 708$); Dep+/–, presence or absence of symptoms of depression (GDS ≥ 6); n, sample size; n.s., non-significant results; *No contrasts/*post hoc* tests performed; χ^2, chi-square or Kruskal-Wallis statistic; η^2, eta-squared, p, *p*-value. Pairwise comparisons are adjusted for multiple comparisons using Bonferroni correction of the *p*-values.

could be demonstrated [24]. These findings suggest that help seeking status, not memory clinic recruitment per se, may be a risk factor for early amyloid deposition which could tie in with the subtle deficits in memory performance observed in the SCD-HS group. Moreover, we did not find differences in CSF biomarkers or cognitive performance between SCD NHS and controls, suggesting that the SCD-NHS group has lower risk and may reflect higher rates of benign SCD [16–18]. No differences between groups were found in levels of CSF t-tau or p-tau. This is perhaps not surprising, as increased levels of t-tau and p-tau are associated with substantial formation of neurofibrillary tangles and neuronal loss which may happen downstream from amyloid deposition and herald the onset of clinical cognitive impairment at later stages [45]. It has been suggested that weakening of memory performance is at first related to $A\beta_{1\text{-}42}$ levels, and progressive loss of neurons and the formation of neurofibrillary tangles is associated with disease severity and progression to dementia [46]. Indeed, several studies have suggested that the presence of amyloid pathology in SCD is the strongest predictor of future cognitive decline [11–13].

Both SCD-HS and SCD-NHS groups had increased levels of depressive symptoms compared to controls. The increase in symptoms may reflect the psychological strain of experiencing cognitive difficulties regardless of brain pathology. However, levels of depressive symptoms as measured by the GDS-15 were significantly higher in SCD-HS. Additional analyses revealed that this group indeed comprised a high rate of individuals with above threshold (GDS-15$\geq$6) symptoms of depression ($n = 12$, 18%). However, none of these individuals harbored amyloid pathology, suggesting that symptoms of depression may not be strongly associated with AD in its preclinical phases and also that symptoms of depression in these cases are not due to the strain of experiencing incipient AD.

While memory performance has shown to predict later cognitive decline and future dementia onset [47, 48], deficits in cognitive performance is also a core feature in clinical depression [49]. Cognitive deficits in depression have been reported within a number

of cognitive domains including executive functioning, attention, learning, memory, and psychomotor speed [50–52]. Interestingly, while we found poorer memory function in help-seeking SCD cases as compared to non-help-seekers, additional analyses could not distinguish SCD help-seekers with symptoms of depression from help-seekers with amyloid plaques with regard to cognitive performance in neither memory domains nor other cognitive domains. However, there are conflicting results regarding which domains of cognition are selectively affected in clinical depression [53–57].

As most SCD cases are benign, or not caused by degenerative brain disease [17], it has been suggested that SCD may be associated with depression, rather than preclinical AD [58, 59]. While it has been reported that presentation of SCD may correlate with depression rather than objective cognitive decline [60, 61], the link between SCD and depressive symptoms has not been universally supported [62, 63].

Nonetheless, it has been reported that prior history of depression is associated with increased risk of developing AD [64]. Indeed, clinical depression is associated with AD later in the disease trajectory [65, 66], and an association between amyloid pathology and late-life depression has been found in several studies [67–70]. However, recent studies have demonstrated that this may not be the case in the preclinical phase of AD. Perin et al. [71] showed that incidence of clinical depression, as determined by the GDS-15, was not increased in cognitively normal individuals with amyloid plaques. Similarly, Donovan et al. [72] showed that an increased level of depressive symptoms was not associated with the presence of amyloid plaques in cognitively healthy cases. These results tie in with our findings, as we did not find an association between amyloid plaques and symptoms of depression in SCD cases. However, this does not dismiss a relationship between AD pathology and clinical depression as the disease progresses.

Although clinical depression and preclinical AD may not be linked, several studies have suggested that subthreshold symptoms of depression and anxiety may be manifestations of preclinical AD [73–75]. Subthreshold levels of depression could be related to worry due to self-perceived reduction in cognition, rather than reflecting clinical depression, in that awareness of SCD causes depressive symptoms which explains increases in distress [76]. Several studies have shown that worried individuals with SCD have an increased risk of developing objective cognitive decline [6, 28, 29, 77]. However, Chen, et al. [62] recently showed that individuals with amyloid plaques, self-reported memory difficulties or memory concerns and not depression or anxiety, were associated with self-awareness of actual worsening in memory function [62]. In our sample, memory was the most frequent SCD complaint, regardless of help-seeking status. This ties in with findings showing that worry is associated with an increased risk of dementia rather than the mere presence of memory complaints [77]. Taken together, this suggests that specific concerns regarding cognition, not subthreshold levels of depression or anxiety, may confer increased risk of clinical progression. These reports are in accordance with our findings showing that help-seeking due to SCD with amyloid plaques may reflect worry or concerns due to a subtle deficit in memory function which is unrelated to symptoms of depression.

We also identified individuals with neither amyloid plaques nor symptoms of depression among the help-seeking group with subtle memory deficits, perhaps reflecting a different type of pathology such as preclinical Lewy body dementia [78], earlier stages of preclinical AD not yet identified using conventional CSF biomarker cut-offs for amyloid pathology (i.e., pre-plaque amyloid dysmetabolism) or perhaps comprising of worried participants with normal age-related memory decline without the presence of neurodegenerative brain disease [79]. This finding also points to a central limitation of our study, which is confined to a cross sectional design and information of progression is therefore lacking. A longitudinal design is needed to assess whether help-seeking SCD cases with amyloid plaques progress to AD-type MCI or dementia, and if participants without amyloid plaques with, or without symptoms of depression will regress or progress with regards to depressive symptoms, SCD, and cognitive performance. Moreover, we did not include information about whether help-seeking was caused by subjective worry due to SCD, or if individuals sought help for other reasons, i.e., having a family history of AD, or informant concern. Unfortunately, due to a lack of available informant reports, this data was not included in our analysis. It has been shown that informant concern may be a better predictor than self-concern of objective cognitive decline [80], and it has been argued that many patients may not express their concern to their GPs [81]. Consequently, non-help-seeking SCD also includes cases with AD pathology,

albeit with different reasons for not seeking medical help.

Conclusions

Our findings shed light on the relationship between depressive symptoms and preclinical AD, which may inform researchers including at-risk cases for interventions studies, as well as GPs seeing cognitively healthy, but worried patients with SCD. While our results support the idea that individuals with SCD seeking help may be at higher risk of AD, SCD help-seekers also included younger individuals with symptoms of depression without amyloid plaques as well as individuals with neither symptoms of depression nor amyloid plaques. These subgroups could not be distinguished based on performance on neuropsychological tests, and longitudinal studies are needed to ascertain the clinical progression of SCD help-seekers with regards to the presence or absence of symptoms of depression and amyloid plaques.

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