Characteristics of subjective cognitive decline associated with amyloid positivity

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FEATURED ARTICLE

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Abstract

Introduction: The evidence for characteristics of persons with subjective cognitive decline (SCD) associated with amyloid positivity is limited.

Methods: In 1640 persons with SCD from 20 Amyloid Biomarker Study cohort, we investigated the associations of SCD-specific characteristics (informant confirmation, domain-specific complaints, concerns, feelings of worse performance) demographics, setting, apolipoprotein E gene (*APOE*) ε4 carriership, and neuropsychiatric symptoms with amyloid positivity.

Results: Between cohorts, amyloid positivity in 70-year-olds varied from 10% to 76%. Only older age, clinical setting, and *APOE* ε4 carriership showed univariate associations with increased amyloid positivity. After adjusting for these, lower education was also associated with increased amyloid positivity. Only within a research setting, informant-confirmed complaints, memory complaints, attention/concentration complaints, and no depressive symptoms were associated with increased amyloid positivity. Feelings of worse performance were associated with less amyloid positivity at younger ages and more at older ages.

Discussion: Next to age, setting, and *APOE* ε4 carriership, SCD-specific characteristics may facilitate the identification of amyloid-positive individuals.

KEYWORDS
Alzheimer's disease, amyloid, cerebrospinal fluid, positron emission tomography, subjective cognitive decline

1 | INTRODUCTION

Cognitively normal persons with evidence of cerebral amyloidosis, as measured with positron emission tomography (PET) or cerebrospinal fluid (CSF), are considered an early stage of Alzheimer's disease (AD), that is, preclinical AD.[1,2] These persons are at an increased risk of developing AD-type dementia.[3,4] Identification of preclinical AD is important for the development of treatments that aim to preserve cognitive function. Cognitively unimpaired persons experiencing subjective cognitive decline (SCD) are also at an increased risk of developing dementia.[5,6] SCD is characterized by perceived cognitive decline in the absence of cognitive impairment.[7] It has been hypothesized that SCD may be an early manifestation of amyloidosis, and practical, low-cost characteristics of SCD could aid in the identification of potential at-risk participants. However, previous studies have shown conflicting results on whether SCD is a specific indicator of amyloidosis, and improved understanding of the association of SCD-specific characteristics with amyloid positivity is needed.

Some studies reported an association between memory complaints or concerns and presence of amyloid pathology,[8–11] whereas others reported similar levels of amyloid pathology in cognitively normal individuals with and without SCD.[3,12] These inconsistent findings may be due to heterogeneity in the definition and assessment of SCD and specific complaints[13] and in the underlying causes of SCD. In an attempt to reduce part of this heterogeneity between studies, Jessen et al.[13,14] suggested characteristics to be collected in studies on SCD that are assumed to increase the likelihood of the presence of amyloid pathology in persons with SCD, such as memory complaints rather than attention/concentration complaints, concerns associated with SCD, and informant confirmation of complaints.[13,14] It remains unknown whether these SCD-specific enrichment characteristics for preclinical AD are associated with amyloid positivity across studies. Furthermore, the characteristics suggested for studies on SCD also included more general risk factors for amyloidosis such as older age,[15,16] apolipoprotein E gene (*APOE*) ε4 carriership,[15] and the presence of neuropsychiatric symptoms,[17] which may further influence the potential associations between SCD characteristics and amyloid positivity, as well as study setting.[6,18] Previous studies examining the association of characteristics of persons with SCD with amyloid positivity were performed within a single cohort[19,20] or focused on age and *APOE* ε4 carriership as characteristics of persons with SCD.[10,11]

This study investigates which general and SCD-specific characteristics are associated with amyloid positivity using individual participant-level data from 20 cohorts included in the Amyloid Biomarker Study.[3,21] In addition, sources of heterogeneity in amyloid positivity between cohorts are examined.

RESEARCH IN CONTEXT

1. **Systematic review**: Previous inconsistent findings on subjective cognitive decline (SCD) as a specific indicator of amyloid positivity, with some studies reporting an association of SCD with amyloid and others reporting no association, may be due to heterogeneity in the definition of SCD and specific complaints. Improved understanding of associations of SCD-specific characteristics with amyloid positivity is needed.
2. **Interpretation**: We observed variability in the frequency of amyloid positivity between cohorts ranging from 10% to 76% when estimated at age 70, which was partly attributable to setting and apolipoprotein E gene (*APOE*) ε4 carriership. In addition to age, setting, and *APOE*-ε4 carriership, we found associations between amyloid positivity and informant confirmation of complaints, memory complaints, attention/concentration complaints, feelings of worse performance, and depressive symptoms. These associations were found mainly in a research setting.
3. **Future directions**: Future research areas are longitudinal relationships of SCD characteristics with amyloid and other AD biomarkers, and associations with clinical progression.

HIGHLIGHTS

- We examined subjective cognitive decline characteristics associated with amyloid.
- Large variability exists in amyloid positivity between cohorts of persons with subjective cognitive decline (SCD).
- Older age, memory clinic setting, and apolipoprotein E gene (*APOE*) ε4 carriership were related to amyloid positivity.
- A number of SCD-specific characteristics were also related to amyloid positivity.
- SCD-specific characteristics may facilitate identifying amyloid-positive persons.

2 | METHODS

2.1 | Participants

Participants were selected from the Amyloid Biomarker Study, an ongoing worldwide data-pooling initiative that collects data from cohorts using amyloid biomarkers on PET or CSF.[3,21] The aim of the Amyloid Biomarker Study is to obtain a better understanding of the pathophysiology of AD. Study selection and data collection are described in Jansen et al.[3] For the current analyses, we included 1640 participants with SCD from 20 cohorts (Table 1). All participants experienced cognitive decline in the absence of objective decline on neuropsychological assessment, and each participant was classified as SCD either based on presentation to a memory clinic or upon assessment. In research settings, participants were typically classified as SCD based

TABLE 1 Data availability for the different measures

Measure	N individuals	N cohorts
Age	1640	20
Sex	1640	20
Education	1481	20
APOE ε4 carriership	1354	16
Setting	1639	20
Memory-specific complaints	1133	18
Attention/concentration-specific complaints	688	11
Informant confirmation of complaints	693	12
Concerns or worries about the complaints	684	9
Feelings of worse performance compared to others of the same age group	1144	13
Symptoms of depression	1257	19
Symptoms of anxiety	1015	17

Abbreviation: APOE, apolipoprotein E gene.

on an interview or questionnaire. In clinical settings, SCD was classified based on a clinical interview, a questionnaire, or a multidisciplinary consensus meeting (Supplemental Table 3). Characteristics of the included cohorts are displayed in Supplemental Table 1. Written informed consent to participate was obtained from all participants and data were de-identified by the respective cohorts. Study protocols were approved by the respective local ethics committees.

2.2 | Measures

2.2.1 | Amyloid assessment

Our primary outcome measure was amyloid beta (Aß) deposition measured by PET or CSF biomarkers, dichotomized as normal and abnormal using study-specific cut-offs or upon visual read for PET (Supplemental Table 2). Amyloid positivity was assessed using amyloid-PET in 499 participants (six cohorts) and using amyloid ß1-42 level in CSF in 1141 participants (15 cohorts). When both PET and CSF amyloid measures were available, we selected the modality that resulted in the greatest number of participants for each cohort for the primary analyses.

2.2.2 | AD risk factors and SCD-specific characteristics

We examined risk factors previously associated with AD and SCD-specific characteristics. The AD risk factors included age, sex, education, setting, presence of *APOE* ε4 genotype, and symptoms of depression and anxiety. SCD-specific characteristics included[13] memory-specific complaints, attention/concentration-specific complaints, informant confirmation of complaints, concerns about the complaints, and feelings of worse cognitive performance compared to others of the same age group. Not all characteristics were available for all cohorts, as shown in Table 1. Education was dichotomized as lower or higher than the total sample median of 14 years. Setting was defined as clinical if patients presented with cognitive complaints at a health care facility or as research if participants were asked to participate in research and recruited through advertisements or from other departments within the health care facility. All SCD-specific characteristics were dichotomized as present or absent. Supplemental Tables 3 and 4 show the definition of SCD and measurement details for each of these characteristics for the different cohorts.

2.3 | Statistical analyses

Differences in AD risk factors and SCD-specific characteristics between amyloid-positive and amyloid-negative participants were analyzed using independent samples *t* tests for continuous variables and χ^2 tests for categorical variables. Generalized estimating equations (GEEs) were used to examine the combined individual participant-level data from different cohorts, and GEEs allow for modeling non-independencies in the data such as clustering of participants within cohorts.[21–23] A logit link function for binary outcome with an exchangeable correlation structure was assumed to account for within-cohort correlation. First, we examined heterogeneity in amyloid-positivity frequencies between the different cohorts. Second, we examined the association of each AD risk factor and SCD-specific characteristic with the frequency of amyloid positivity in separate, uncorrected GEE analyses. Third, we combined all significant characteristics in one GEE model and examined the effect of the remaining characteristics by adding them one-by-one separately to the GEE model and by testing two-way interaction effects with the significant characteristics from analysis 2. For any interaction effect with one of the significant characteristics from analysis 2, we calculated stratified mean predicted values for various levels of the individual characteristics (eg, for different ages, for *APOE* ε4 carriers vs non-carriers, or for research vs clinical settings). Nonsignificant terms were removed step by step for each model based on the highest *P*-values. Terms were retained in each model equation when the Wald statistic was significant ($P < .05$). Significant terms in each model are described in Supplemental Table 5. Additional analyses included examining discrepancies in amyloid positivity between PET and CSF measures and examining discrepancies between self- and informant-reported complaints. All analyses were performed using SPSS statistical software, version 26 (IBM Corp).

3 | RESULTS

We included 1640 participants with SCD (mean age 66.8 (SD 7.95) years), of which 863 (53%) were women and 363 (21%) were

TABLE 2 Sample characteristics according to amyloid status

	All	Amyloid negative	Amyloid positive
N individuals	1640	1277	363
Age, y (SD)	66.8 (7.95)	66.1 (7.91)	69.2 (7.61)**
Education, N (%) low (< 14 years)	810/1481 (55)	618/1144 (54)	192/337 (57)
MMSE, N, mean (SD)	1141, 28.6 (1.64)	849, 28.6 (1.62)	292, 28.6 (1.69)
Sex, N (%) women	863/1640 (53)	677/1277 (53)	186/363 (51)
p-tau positive, N (%)	357/1093 (33)	237/839 (28)	120/254 (47)**
*APOE ε*4 carrier, N (%)	464/1354 (34)	303/1074 (28)	161/208 (58)**
Setting, N (%) memory clinic	1108/1639 (68)	822/1276 (64)	286/363 (79)**
Memory-specific complaints, N (%) yes	702/1133 (62)	534/884 (60)	168/249 (68)
Attention/concentration-specific complaints, N (%) yes	261/952 (38)	193/553 (35)	68/135 (50)*
Informant confirmation of complaints, N (%) yes	377/693 (54)	292/559 (52)	85/134 (63)*
Concerns or worries about the complaints, N (%) yes	492/684 (72)	399/558 (72)	93/126 (74)
Feelings of worse performance compared to others of the same age group, N (%) yes	501/1144 (44)	349/901 (44)	107/243 (44)
Symptoms of depression, N (%) yes	227/1257 (18)	185/980 (19)	42/277 (15)
Symptoms of anxiety, N (%) yes	166/1015 (16)	132/791 (17)	34/224 (15)

Note: N is displayed as N/total available N for each characteristic, % is the percentage within the available N.
SD, standard deviation; APOE, apolipoprotein E; p-tau, phosphorylated tau.
*$P < .05$ or.
**$P < .001$ for difference between amyloid positive persons and amyloid-negative persons. Data availability for the different measures is shown in Table 1.

amyloid positive. This is comparable to the observed prevalence of amyloid positivity in 697 participants with SCD included in our previous study (22% in CSF and 23% in PET).[23] Table 2 shows sample characteristics according to amyloid status. Compared with amyloid-negative persons, amyloid-positive persons were older, more often CSF phosphorylated tau (p-tau) positive, more often *APOE ε*4 carriers, more often recruited from a memory clinic setting, more often had attention/concentration complaints, and informants more often confirmed their complaints.

3.1 | Heterogeneity in amyloid positivity

Figure 1 demonstrates heterogeneity between cohorts in age-related frequencies of amyloid positivity for persons with SCD. There was considerable heterogeneity, as mean amyloid positivity estimates at age 70 ranged from 10% to 76% (Supplemental Table 6).

3.2 | Associations with amyloid positivity

In univariate analyses with AD risk factors, older age (18% at age 60, 27% at age 70, and 39% at age 80; $P < .001$), a memory clinic setting (28% vs 17% for research setting, $P = .008$), and *APOE ε*4 carriership (37% vs 16% for *APOE ε*4 non-carriers, $P < .001$) were associated with higher frequencies of amyloid positivity, whereas sex, education, and symptoms of depression and anxiety were not (Figure 2, Supplemental Table 5, analysis 1 and analysis 2). None of the SCD-specific characteristics were associated with amyloid positivity in these univariate analyses.

Because the AD risk factors age, setting, and *APOE ε*4 carriership were associated with amyloid positivity in the univariate analyses, we next performed multivariate analyses including age, setting, and *APOE ε*4 carriership, and we tested separately for each variable that was not significant in the univariate analyses whether they had an association with amyloid positivity or an interaction effect with one of these three factors. We found a higher frequency of amyloid positivity in persons with a lower education (28% at age 70, vs 23% for higher education, $P < .001$, Figure 3E and Supplemental Table 5, analysis 3).

In addition, the associations of informant confirmation of complaints, memory complaints, attention/concentration complaints, and depressive symptoms with amyloid positivity were dependent on setting ($P < .001$ for informant confirmation of complaints, $P < .001$ for memory complaints, $P < .001$ for attention/concentration complaints, and $P = .035$ for depressive symptoms, Supplemental Table 5, analysis 3). Within a research setting, amyloid positivity was higher if complaints were confirmed by an informant (21% at age 70) compared to those without confirmation (8%, Figure 3A and Supplemental Figure 1A), higher in persons with complaints specific to memory (25% at age 70) compared to persons without complaints specific to memory (9%, Figure 3B and Supplemental Figure 1B), higher in persons with complaints specific to attention/concentration (34% at age 70) compared to persons without complaints specific to attention/concentration (14%, Figure 3C and Supplemental Figure 1C), and higher in persons without depressive symptoms (17% at age 70) compared to persons with depressive symptoms (8%, Figure 3D and Supplemental Figure 1D).

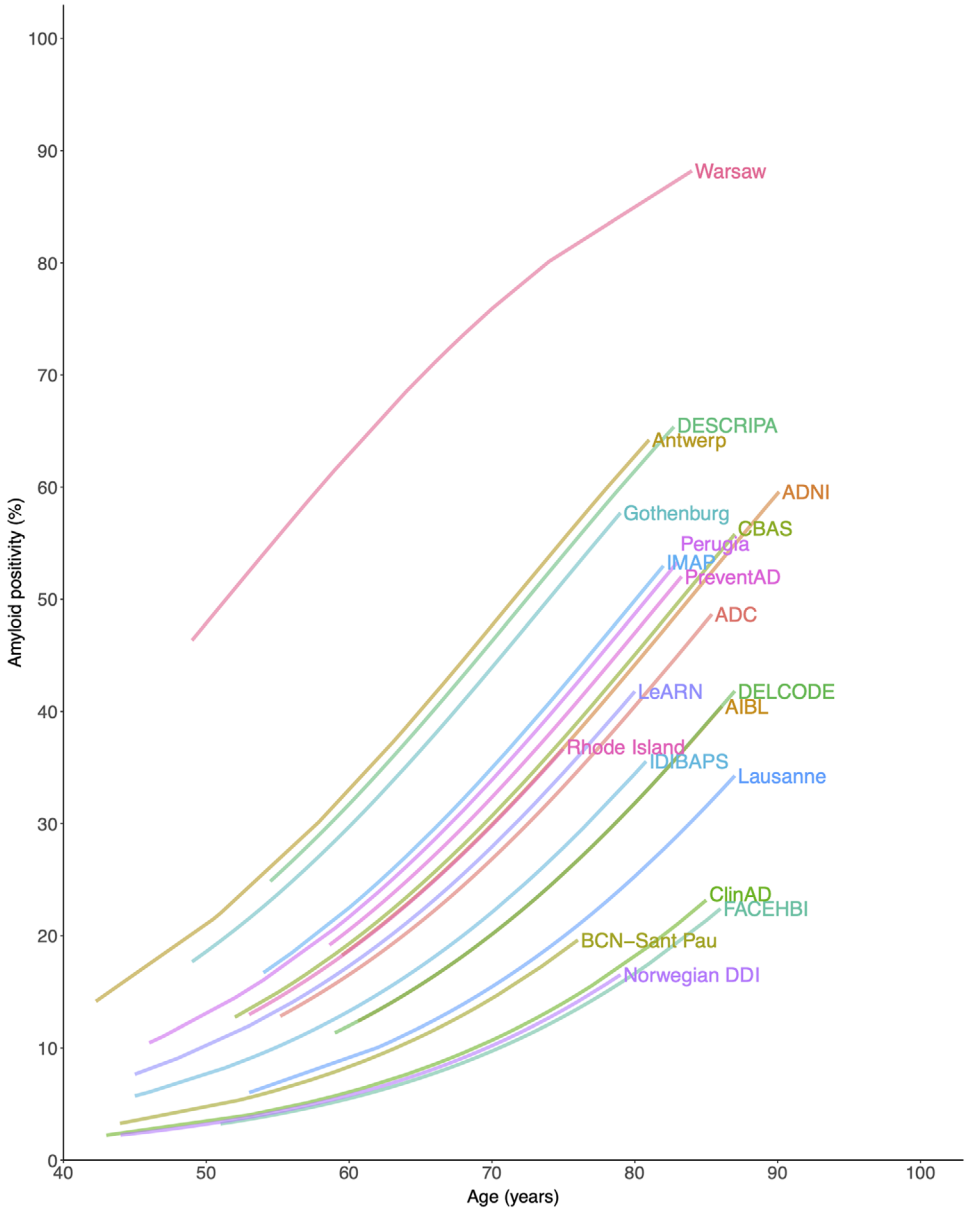

FIGURE 1 Heterogeneity in amyloid positivity between the included cohorts. Note: Prevalence of amyloid positivity is shown on the Y-axis and age is shown on the X-axis. Each line represents a different cohort. Characteristics of the different cohorts are described in Supplemental Table 1

Within a memory clinic setting, informant confirmation of complaints, memory complaints, attention/concentration complaints, and depressive symptoms were not associated with amyloid positivity.

Furthermore, the influence of feelings of worse performance was dependent on age ($P = .005$). In younger persons, feelings of worse performance were associated with a lower frequency of amyloid positivity (at age of 50: 4% with feelings of worse performance, vs 7% without feelings of worse performance, $P = .017$), whereas in older persons, feelings of worse performance were associated with a higher frequency of amyloid positivity (at age 90: 68% with feelings of worse performance, vs 50% without feelings of worse performance, $P = .021$, Figure 3F and Supplemental Figure 1F). No associations with amyloid positivity were found of sex, anxiety, and concerns about the complaints.

The number of participants for which data were available for each combination of characteristics is shown in Supplemental Table 7. Figure 4 is a heat map showing the estimated frequency of amyloid positivity based on combinations of characteristics (associated confidence intervals are displayed in Supplemental Table 8). The heat map visualizing the frequency of amyloid positivity by age, setting, *APOE* ε4 carriership, and other SCD characteristics may assist interpretation of our findings. For example, in 70-year-olds, the frequency of amyloid positivity was lowest in *APOE* ε4 non-carriers in a research setting without informant confirmation of complaints (3%) and highest in *APOE* ε4 carriers in a memory clinic setting with lower educational attainment (54%). Although differences were relatively small compared with the effects of age, setting, and *APOE* ε4 carriership, the estimates differed

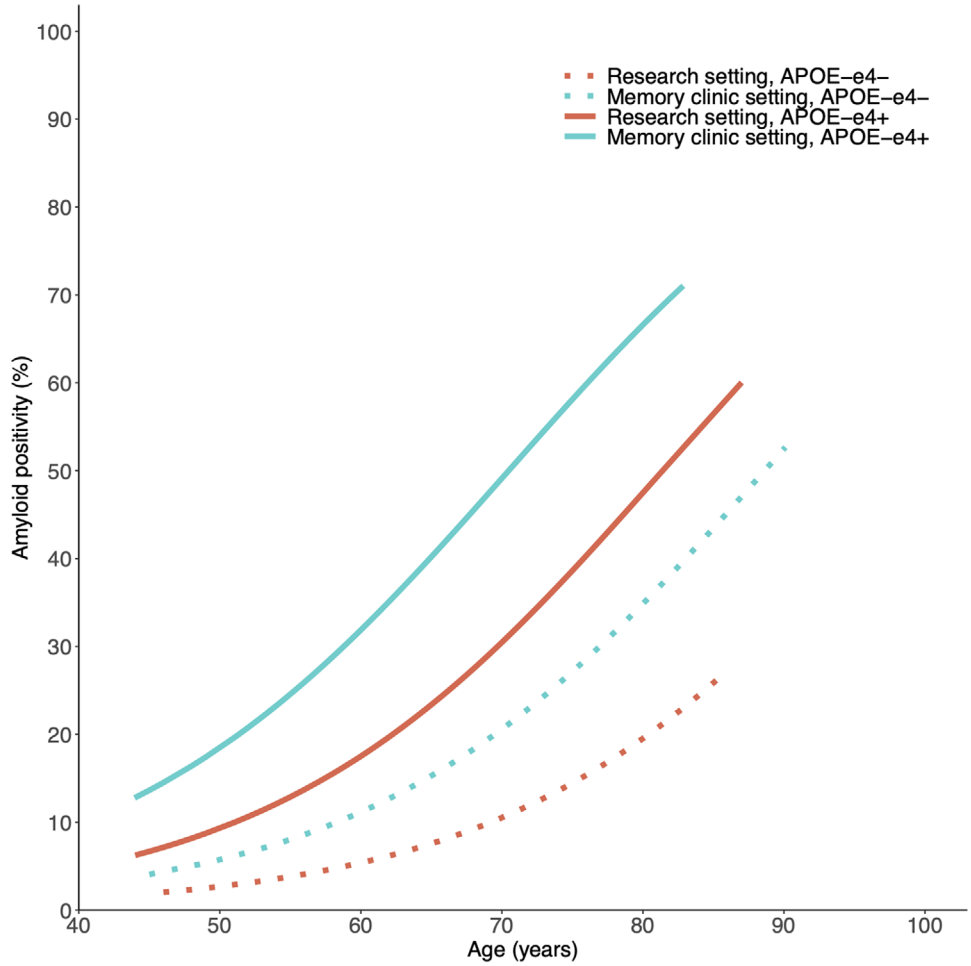

FIGURE 2 Amyloid positivity by age, setting, and *APOE* ε4 carriership. Note: Frequency of amyloid positivity for individuals with SCD is shown on the Y-axis, and age is shown on the X-axis. Each line represents a different combination of *APOE* ε4 carriership and setting. Number of participants included for each combination is shown in Supplemental Table 8

up to 31% for persons with versus without specific SCD characteristics with similar age, setting, and *APOE* ε4 carriership.

3.3 | Sensitivity analyses

3.3.1 | Heterogeneity when taking into account age, setting, and *APOE* ε4 carriership

Supplemental Figure 2 demonstrates heterogeneity in amyloid-positivity frequencies between the included cohorts, when taking into account age, setting, and *APOE* ε4 carriership. Variability in amyloid positivity between cohorts was larger in cohorts from a memory clinic setting than from a research setting (estimates at age 70 ranged from 7% to 73% for *APOE* ε4 non-carriers in a memory clinic setting [11 cohorts] vs 2% to 19% for *APOE* ε4 non-carriers in a research setting [6 cohorts]) and ranged from 23% to 91% for *APOE* ε4 carriers in a memory clinic setting [11 cohorts] vs 6% to 45% for *APOE* ε4 carriers in a research setting [6 cohorts]).

3.3.2 | Influence of amyloid biomarker modality

No difference was found in the in age-related frequency of amyloid positivity by biomarker modality. The frequency of amyloid positivity at age 70 was 26% (20% to 33% confidence interval) based on PET, and 28% (22% to 35% confidence interval, $P = .556$) based on CSF. Sample sizes did not allow examining the association of each characteristic with amyloid positivity based on PET or CSF separately.

3.3.3 | Discrepancy between self-reported and informant-reported complaints

Discrepancy between self-reported memory complaints and informant confirmation of complaints occurred in 170 individuals (reported in 546 participants from nine cohorts), but was not associated with amyloid positivity in the model, including age, setting, and *APOE* ε4 carriership (16% for discrepancy vs 15% for no discrepancy, $P = .443$).

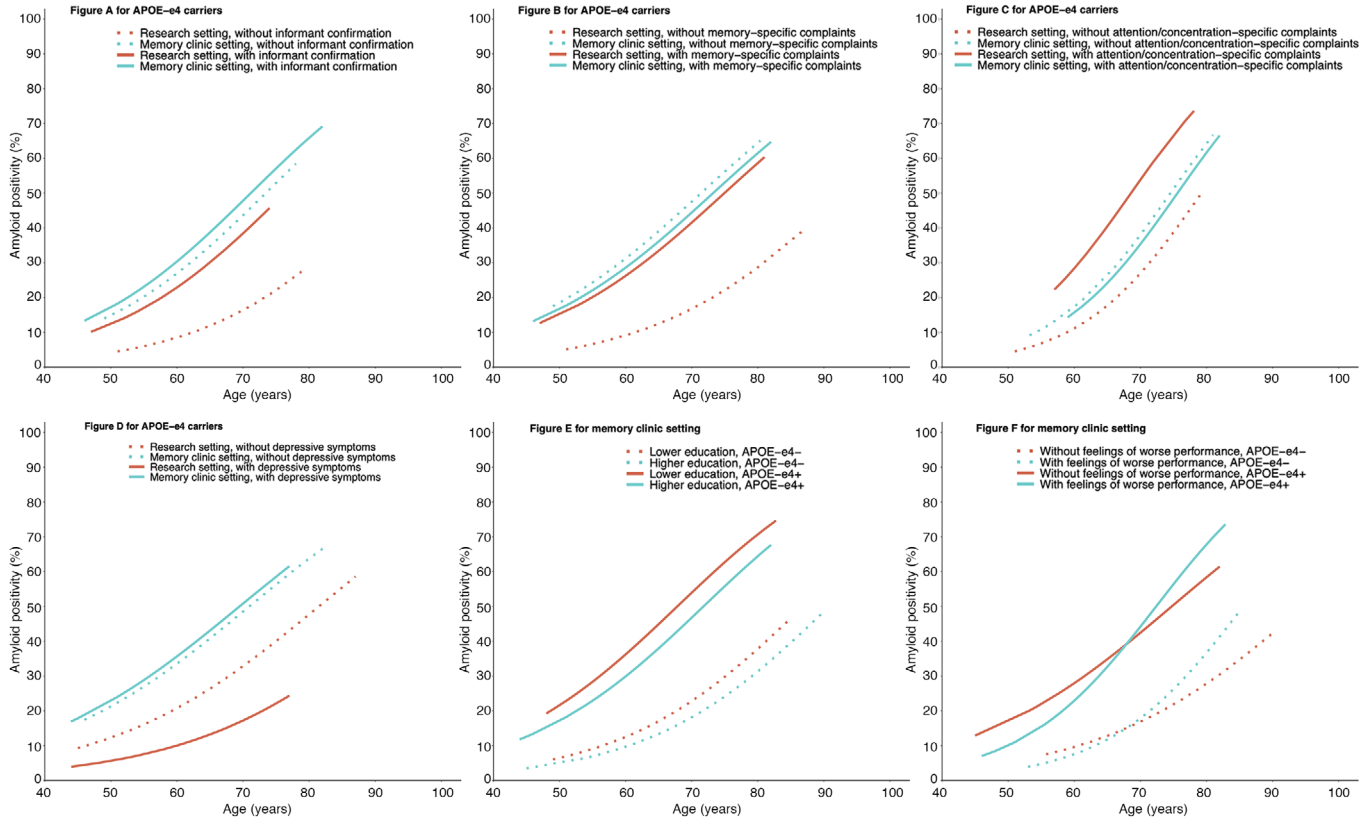

FIGURE 3 Amyloid positivity by age within *APOE* ε4 carriers (A-D) according to different subgroups of setting and informant confirmation (3A), setting and memory complaints (3B), setting and attention/concentration complaints (3C), or setting and depression (3D); and amyloid positivity by age within a memory clinic setting according to different subgroups of *APOE* ε4 carriership and education (3E), or *APOE* ε4 and feelings of worse performance (3F). Note: (A–D) show interaction with setting, and (E and F) show interactions with *APOE* ε4 carriership or age. A was based on the model including age, setting, *APOE* ε4 carriership, and informant confirmation of complaints, and shows estimated amyloid positivity for *APOE* ε4 carriers only. (B) was based on the model, including age, setting, *APOE* ε4 carriership, and complaints specific to memory, and shows estimated amyloid positivity for *APOE* ε4 carriers only. (C) was based on the model, including age, setting, *APOE* ε4 carriership, and complaints specific to attention/concentration, and shows estimated amyloid positivity for *APOE* ε4 carriers only. (D) was based on the model including age, setting, *APOE* ε4 carriership, and depressive symptoms, and shows estimated amyloid positivity for *APOE*-ε4 carriers only. (E) was based on the model including age, setting, *APOE* ε4 carriership, and education, and shows estimated amyloid positivity for a memory clinic setting only. (F) was based on the model including age, setting, *APOE* ε4 carriership, and feelings of worse performance, and shows estimated amyloid positivity for a memory clinic setting only. Results shown in (A–D) show a similar pattern for *APOE* ε4 non-carriers, and results shown in (E and F) show a similar pattern for persons in a research setting (Supplemental Figure 1A-1F). Data for each combination of characteristics are shown in Supplemental Table 7

4 | DISCUSSION

The present study examined the association of different AD risk factors and SCD-specific characteristics with amyloid positivity in a large sample of 1640 participants with SCD from 20 cohorts. We found that in individuals with SCD, only older age, a memory clinic setting, and *APOE* ε4 carriership were univariately associated with amyloid positivity, and none of the SCD-specific characteristics. When adjusting for these three factors, lower education was associated with increased amyloid positivity. The associations of the SCD-specific characteristics informant confirmation of complaints, memory complaints, attention/concentration complaints, and depressive symptoms with amyloid positivity were dependent on setting and were found within a research setting only. The association of feelings of worse performance depended on age: there was a higher frequency of amyloid positivity at older ages and a lower frequency at lower ages.

We noted a large variability in the frequency of amyloid positivity between cohorts ranging from 10% to 76% when estimated at age 70. This indicates that SCD indeed is a heterogeneous concept and the concept itself does not seem to be a predictor of amyloid positivity. We found that part of this heterogeneity can be attributed to age, setting, and *APOE* ε4 carriership. Older age, a memory clinic setting, and *APOE* ε4 carriership were associated with a higher frequency of amyloid positivity, which is in line with previous studies.[6,15]

When adjusting for age, setting, and *APOE* ε4 carriership, we found that higher education was associated with a lower frequency of amyloid positivity, which is in accordance with a lower risk for AD-type dementia in persons with a higher educational attainment but conflicts with the general explanation that education lowers the risk of developing dementia by compensation of the effects of brain pathology.[24,25] In our previous study,[3] we reported an increased frequency of amyloid positivity with higher education in persons with normal cognition,

Other characteristics		Main characteristics: Age 60, APOE-ε4 non-carrier, Research setting	Age 60, APOE-ε4 non-carrier, Memory clinic setting	Age 60, APOE-ε4 carrier, Research setting	Age 60, APOE-ε4 carrier, Memory clinic setting	Age 70, APOE-ε4 non-carrier, Research setting	Age 70, APOE-ε4 non-carrier, Memory clinic setting	Age 70, APOE-ε4 carrier, Research setting	Age 70, APOE-ε4 carrier, Memory clinic setting	Age 80, APOE-ε4 non-carrier, Research setting	Age 80, APOE-ε4 non-carrier, Memory clinic setting	Age 80, APOE-ε4 carrier, Research setting	Age 80, APOE-ε4 carrier, Memory clinic setting
Education	Lower	5.8*	12.5*	19.8*	35.4**	11.3**	22.8**	33.7**	53.9**	20.9**	37.6**	51.1**	72.2**
	Higher	4.4	9.7	15.6	29.4	8.8	18.1	27.6	46.8	16.5	32.0	45.8	65.1
Informant confirmation of complaints	No	1.6**	6.0	8.5**	28.4	3.3**	11.7	16.4**	43.7	6.7**	21.8	27.7**	58.4
	Yes	4.9	7.0	22.9	30.3	9.8	13.7	38.5	47.8	18.5	25.0	*NA*	62.5
Memory-specific complaints	No	2.2**	9.3	9.2**	30.8	4.3**	16.6	16.8**	47.4	8.3**	28.2	28.7**	64.7
	Yes	7.4	8.3	26.2	28.6	13.8	15.2	41.5	44.4	24.2	26.2	60.3	61.5
Attention/concentration -specific complaints	No	2.4**	3.9	10.7**	18.8	6.7**	10.6	26.9**	35.5	17.4**	26.0	49.3**	66.7
	Yes	7.9	3.5	28.4	14.3	18.6	9.4	52.6	35.2	33.2	24.6	70.5	64.1
Feelings of worse performance	No	5.2*	9.6*	16.5*	27.6*	9.4*	16.5	27.3	42.3	16.4	27.8	40.2	58.4
	Yes	4.0	7.6	13.2	22.9	10.0	17.6	28.8	44.1	22.8	37.6	51.8	69.9
Depression	No	7.0*	12.3	20.8*	33.1	12.2*	20.8	32.9*	48.6	20.7*	32.7	43.1*	61.0
	Yes	3.1	13.5	10.0	35.8	5.6	22.5	17.2	50.8	10.0	36.1	24.4	61.5

FIGURE 4 Heat map showing the mean predicted amyloid positivity by age, setting, *APOE* ε4 carriership, and significant characteristics from analysis 3. Note: Green colors indicate lower frequencies of amyloid positivity, and red colors indicate higher frequencies of amyloid positivity. Table columns contain the main characteristics age, setting, and *APOE* ε4 carriership, and rows contain additional characteristics that were associated with lower or higher frequency of amyloid positivity. Results are displayed for age 60, 70, and 80. Some of the combinations of characteristics were not available for persons age60, 70, or 80 and a slightly younger or older age was selected in 9% of the combinations (range from 3 years younger to 1 year older). *$P < .05$ or **$P < .001$ for difference between row characteristic (lower education vs higher education, without vs with informant confirmation of complaints, without vs with complaints specific to memory, without vs with complaints specific to attention/concentration, without vs with feelings of worse performance, without vs with depressive symptoms, respectively).

but we did not separately examine associations of education with amyloid positivity in persons with SCD. Furthermore, higher educational attainment was more frequent in the group of persons without SCD (64% >14 years) compared to our present sample of persons with SCD (45% >14 years), and none of the participants with normal cognition were from a memory clinic setting.

Some SCD-specific characteristics were associated with amyloid positivity only in a research setting. Memory complaints as opposed to complaints in non-memory domains, attention/concentration-specific complaints, and informant confirmation of complaints were indicative of amyloid positivity in a research setting only. Although previous studies that were conducted within a single research or clinical setting reported associations of memory complaints[8,20,26] and informant confirmation of complaints[20,27] with amyloid positivity, we did not observe such associations in our analyses. Possibly the lack of discriminative value of these characteristics in a memory clinic setting results from the fact that memory complaints and informant confirmation are common in this setting (Supplemental Table 7). Moreover, a previous single-center study did not find an association of attention/concentration complaints with amyloid positivity, whereas we did observe an association.[28] Because the single-center study corrected for age, sex, education, and depressive symptoms, direct comparisons are difficult. Furthermore, we found that depressive symptoms were associated with a lower frequency of amyloid positivity within a research setting only. Affective disorders are commonly associated with SCD,[13] but affective symptoms have also been associated with incident AD-type dementia in at-risk individuals.[29] The risk of underlying pathophysiology is apparently partly associated with setting and may be related to medical help-seeking.[30]

Of interest, the presence of feelings of worse performance was associated with a higher frequency of amyloid positivity in older persons only. In younger persons, feelings of worse performance might be due to functional cognitive disorders[31] rather than underlying AD pathology. Similar results were described in reviews by Jonker et al.,[32] who found that in younger persons with memory complaints that these complaints generally refer to neuropsychiatric symptoms or personality factors, and Rabin et al.,[33] who also found that underlying causes of complaints vary with age.

Overall, effect sizes of education, informant confirmation of complaints, memory complaints, attention/concentration complaints, depressive symptoms, and feelings of worse performance were relatively small and of limited added value in explaining heterogeneity in amyloid positivity in persons with SCD next to age, setting, and *APOE* ε4 carriership, which showed the strongest effects in our analyses. Most associations of SCD-specific characteristics with amyloid positivity were only seen in a research setting, implicating potential value within research settings. The lack of associations with amyloid positivity of these SCD-specific characteristics in clinical settings could mean that they are of less value within clinical settings.

In the present study, we combined data collected within a large number of cohorts in different settings to examine associations between AD risk factors and SCD characteristics and amyloid positivity. A limitation of our study is that most cohorts only collected data on a subset of characteristics of the subjective complaints. This may be explained

by the fact that most cohorts started data collection before the introduction of the SCD research criteria and that collection of these characteristics has not been fully implemented in clinical and research practice. Therefore, a limitation inherent to our approach is that each analysis included a different sample and that statistical power was relatively small for a number of characteristics. A limitation inherent to combining data from multiple studies is the use of different assessment methods to define each characteristic. Although all assessment methods are transparently shown in Supplemental Table 3, caution is warranted in comparing studies. However, despite considerable heterogeneity, associations were found across the different cohorts. Examining the influence of assessment method (clinical interview vs scale) for the different SCD characteristics was not possible due to the used definitions for SCD characteristics: most studies defined the presence of specific characteristics based on one item from a questionnaire or based on a specific question within a structured interview. Furthermore, sample sizes did not allow analyses stratified by modality, and potential influence of amyloid modality on the associations reported in the present study cannot be excluded. However, no main effect of modality was found in univariate analyses. Finally, the cross-sectional nature of the present study does not allow assessment of stability of the SCD characteristics over time.

5 | CONCLUSIONS AND IMPLICATIONS

Our findings show that next to age, setting, and *APOE ε4* carriership, other characteristics in the context of SCD related to amyloid pathology are education, informant confirmation of complaints, memory complaints, attention/concentration complaints, feelings of worse performance, and depression, but mostly within a research setting only. Our findings show that enrichment characteristics for preclinical AD proposed in the SCD research criteria[13] indeed are associated with amyloid pathology, but these associations often depend on age and setting. Our study also suggests that education is an additional characteristic important to consider in studies on SCD. Inclusion of practical, low-cost AD risk factors, and SCD-specific characteristics aids in the identification of individuals that will likely benefit from disease-modifying treatment. However, the effect sizes of the SCD-specific characteristics were relatively small and of limited added value next to age, *APOE ε4* carriership, and across settings. Because it has been suggested previously that consistency over time of SCD characteristics is associated with a greater risk of future decline,[14,34] the longitudinal relationship between SCD characteristics with amyloid and other AD biomarkers, as well as associations with clinical progression are important areas for future research. Future research might also examine this longitudinal relationship in individuals with evidence of both amyloidosis and tauopathy, since these individuals might be at increased risk of clinical progression.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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