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CEREBROSPINAL FLUID BIOMARKERS

Deciphering the factors that influence participation in studies requiring serial lumbar punctures

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Abstract

Introduction: Cerebrospinal fluid biomarkers increasingly inform the causes of dementia and may provide objective markers of disease progression. There is a need to decipher participant and procedural factors that promote participation in studies incorporating longitudinal biomarker measures.

Methods: Participant and procedural factors associated with participation in longitudinal biomarker studies were determined in individuals enrolled in studies of memory and aging at the Knight Alzheimer Disease Research Center (Saint Louis, MO, USA).

Results: Complications were encountered following 331 of 1484 lumbar punctures (22.3%; LPs), affecting 280 of 929 participants (30.1%); in >95% complications were minor. Three hundred fifteen of 679 eligible participants (46.4%) completed multiple LPs. Younger age (odds ratio [OR] 2.08 per decade [95% confidence interval (CI) 1.61–2.94]), normal cognition (OR 21.4 [2.85–160.1]), and the absence of heart disease (OR 2.0 [1.01–3.85]) or seizures at study entry identified participants with increased odds of completing three or more LPs.

Discussion: Factors influencing participation may be leveraged to improve recruitment and retention within observational and therapeutic studies requiring serial LPs.

KEYWORDS

Alzheimer's disease, biomarker, cerebrospinal fluid, dementia, lumbar puncture

1 | BACKGROUND

Biomarkers are used increasingly to determine the cause of dementia,[1–4] define the biochemical changes that influence rates of disease progression,[5,6] and identify individuals at high risk of developing dementia who may benefit from therapeutic interventions designed to delay or prevent cognitive impairment.[7] Cerebrospinal fluid (CSF) biomarkers are ideal for this purpose, as CSF is sensitive to the early changes associated with the most common cause of dementia, Alzheimer's disease (AD)[8]; can be analyzed simultaneously for multiple analytes that directly reflect biochemical changes within the central nervous system; and can be safely and efficiently sampled from individuals with all levels of cognitive impairment,[9,10] informing the dynamic relationship between biomarkers and symptomatic expression of disease.[11,12]

Despite the high value placed on CSF in research,[13] participants express low enthusiasm for participation in studies requiring lumbar puncture (LP).[14] Several factors contribute to this reticence, including concerns regarding the safety of the procedure.[14,15] Although LP is typically safe, complications are encountered in research and clinical settings. Most commonly, these complications include mild self-limited low-back pain or headache, with medical intervention limited to

the <5% of participants who require an autologous blood patch for the treatment of post-dural puncture headache.[15–20] Prior research in this area has shown that fearfulness of LP is reduced in participants who have previously completed a successful LP,[14] suggesting that these participants should be more willing to participate in subsequent LPs. However, retention within studies requiring serial LPs remains challenging.

There is a need to promote participant enrollment and engagement within research studies requiring serial LPs, yet the factors that influence longitudinal participation are largely unknown. Recognizing this, we evaluated the participant and procedural factors that associated with serial LP completion by community-dwelling participants enrolled within longitudinal studies of memory and aging at the Knight Alzheimer Disease Research Center (ADRC; Washington University School of Medicine; Saint Louis, MO, USA). Emphasis was placed on identifying potentially modifiable factors that could be targeted to promote retention in longitudinal research studies, including prior history of LP complications.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional sources (eg, PubMed). Despite increasing interest in the use of longitudinal biomarker measures in dementia research,[11–13] no studies considered how to promote engagement within studies incorporating serial cerebrospinal fluid (CSF) measures.
2. Interpretation: Age, cognitive status, and health history at study entry independently influenced odds of participation in serial lumbar punctures (LPs) in community-dwelling older adults enrolled in prospective studies of memory and aging. This information can be leveraged to promote recruitment of individuals who are more likely to agree to longitudinal CSF sampling, and to enhance retention of enrolled participants who are likely to decline requests for subsequent LPs.
3. Future directions: Strategies are needed to reduce burden associated with participation in longitudinal biomarker research. Particular attention should be paid to the needs of older, cognitively impaired participants with medical comorbidities.

2 | METHODS

2.1 | Standard protocol approvals, registrations, and patient consents

This nested-cohort study included data from prospectively evaluated community-dwelling individuals enrolled within longitudinal studies of memory and aging at the Knight ADRC between January 2004 and April 2018. Eligible participants completed at least one clinical assessment and research LP, and consented to the use of information and CSF specimens for research purposes. Study procedures and policies were approved by the Washington University School of Medicine Institutional Review Board.

2.2 | Clinical assessments and research lumbar punctures

Beginning in 2004, newly enrolled research participants agreed in principle to undergo an LP for research purposes at study entry and every 3 years thereafter. Exceptions were made for African American participants, with the intent to improve representation within research, irrespective of opportunities to measure CSF biomarkers.

Prior to undergoing an LP, participants were evaluated by experienced clinicians using semi-structured interviews with both the participant and a knowledgeable collateral source, and a detailed neurologic examination of the participant.[21] When appropriate, diagnoses of dementia were rendered by study clinicians, integrating results from the clinical assessment and bedside measures of cognitive function, referencing established diagnostic criteria.[22,23] The severity of cognitive impairment was staged using the global Clinical Dementia Rating (CDR) scale.[24] Participants with moderate or severe dementia (CDR ≥2) were not asked to undergo serial LPs and were excluded from longitudinal analyses. Participants prescribed dual antiplatelet therapies were counseled to hold one anti-platelet agent 7 days before their planned LP. If their prescribing physician deemed this unsafe, an LP was not scheduled and they were excluded from longitudinal analyses. Similarly, LPs were not performed in participants with other known contraindication (eg, space-occupying cerebral lesion, ongoing anticoagulant therapy[25]), and they were excluded from longitudinal analyses.

On the day of the LP, participants were informed of the rationale for the LP and associated risks. Participants were counseled to avoid strenuous activity for 24 hours following the procedure and to hydrate with clear fluids and caffeinated beverages if desired. All participants were instructed to notify study personnel if concerning symptoms or side effects developed following the LP, and were reassured that access to a blood patch would be provided by study-affiliated physicians if required to treat post-dural puncture headache. LPs were completed by experienced neurologists using established protocols in consented individuals.[26] Briefly, LPs were performed in the early morning (between 0730 and 0900 hours) on fasted participants. Unless contraindicated, participants were seated in a massage chair, and local analgesia accomplished with 1% lidocaine injected subcutaneously via a 25-gauge needle. CSF was sampled using a 22-gauge atraumatic ("non-cutting") Sprotte needle, advanced between the L3/L4 or L4/L5 vertebrae. If CSF could not be accessed using standard techniques, the operating clinician could reattempt the procedure with the participant in the lateral decubitus position. Conventional ("cutting") spinal needles (22-gauge) were available upon request by the

operating clinician. Deviances from standard procedures and intraprocedural LP complications were documented prospectively by the study coordinator.

Following the LP, participants were provided with breakfast and observed for 1 hour before discharge home. Participants were encouraged to lie supine throughout the observation period, although this was not strictly enforced. All participants were reached by telephone within 24 hours and queried concerning post-procedural side effects. Additional follow-up calls established the natural history of post-LP complications when necessary. All complaints and concerns were reviewed with study physicians and patients were recommendations for treatment provided when appropriate. Complications that resolved within 24 hours with rest and over-the-counter analgesics were graded as mild (eg, back pain at the site of needle insertion). Moderate complications included those that persisted beyond 24 hours. Complications requiring medical evaluation or physician-directed intervention (namely a blood patch) were graded as severe. Autologous blood patch was offered to any patient who fulfilled International Classification of Headache Disorders Criteria III for post-dural puncture headache,[27] and in whom headache persisted for >24 hours despite implementation of conservative management strategies (rest, hydration, and analgesia). Autologous blood patches were undertaken by experienced anesthesiologists, targeting the general proximity of the prior LP.

2.3 | Data analysis

Demographic, clinical, and LP data were available from all participants who completed one or more research LPs. Additional data concerning apolipoprotein epsilon (APOEε) genotype and AD biomarkers (CSF levels of amyloid β $[A\beta]_{40-42}$, total-tau, and phosphorylated-tau; measured using the Elecsys assay as previously reported[28]) were available from a majority of participants. Participants who were eligible to complete two or more consecutive LPs were defined as "serial completers."

Demographic and clinical details were summarized using descriptive statistics and the frequency of LP complications determined across participants. Demographic and participant and procedural factors associated with post-LP complications and serial completion of LP studies were evaluated using the chi-square or Fisher exact tests for categorical variables and Student t (independent variables) for continuous variables. Variables implicated as potential contributors to post-LP complications or serial completion of LP studies on univariate analyzes ($P < 0.05$) were further evaluated using multivariable logistic regression (forced entry), allowing the effect of variables on the outcome of interest to be quantified while adjusting for confounding variables. Variables were excluded if data were missing from >10% of eligible individuals. Model explanatory power was assessed using the c-statistic (area under the receiver operating characteristic [ROC] curve). Statistical analyses were conducted using SPSS Statistics (IBM Corp., Version 24.0. Armonk, NY). Statistical significance was established at $P < 0.05$.

TABLE 1 Participant characteristics at the time of first lumbar puncture

Participant characteristics	Participants ($n = 929$)
Age, mean (±SD), years	68.7 (9.3)
Sex, female, n (%)	492 (53.0)
Race, n (%)	
Non-Hispanic white	834 (89.8)
African American	86 (9.3)
Other	9 (1.0)
Education, mean (±SD), years	15.9 (2.7)
Cognitive status, n (%)	
Cognitively normal	690 (74.3)
Symptomatic Alzheimer's disease	163 (17.5)
Other dementia	76 (8.2)
APOEε4 carrier, n (%)	355/876 (40.5)

APOE, apolipoprotein; SD, standard deviation.

2.4 | Data availability

Study data are available to qualified investigators upon approval of a resource request by the Knight ADRC Data Request Committee (https://knightadrc.wustl.edu/research/resourcerequest.htm).

3 | RESULTS

3.1 | Participant demographics

Between January 2004 and May 2018, a total of 929 participants completed 1484 LPs. Participant characteristics at the time of their first LP are detailed in Table 1. Participants were well educated, with ages spanning mid-to-late life (range, 42.7- to 99.4-years old). The majority of participants were non-Hispanic white and cognitively normal (CDR 0), and reflected the characteristics of the surrounding community. AD was the most common cause of cognitive impairment (163/239, 68.2%), with most affected participants exhibiting very mild (CDR 0.5; $n = 111$, 68.1%) or mild dementia (CDR 1; $n = 48$, 29.4%) at study entry. Participants with moderate severity AD dementia (CDR 2; $n = 4$, 2.5%) at study entry were not asked to complete subsequent LPs.

3.2 | Lumbar puncture complications

Complications were reported following 331 LPs (22.3%), affecting 280 (30.1%) distinct participants (Table 2). More than 95% of complications resolved within 24 hours without medical intervention and were deemed minor. Severe complications requiring medical intervention were limited to the 38 participants (2.6%) with unremitting post-dural puncture headaches who required autologous blood patches. Univariate comparisons suggested that complications were overrepresented in younger, female, and cognitively normal participants with a history

TABLE 2 Complications reported following 1484 lumbar punctures

Lumbar puncture complications	*n* (%)
Headache[a]	166 (11.2)
Mild	115 (7.7)
Moderate	13 (0.9)
Severe	38 (2.6)
Back pain	141 (9.5)
Vasovagal response	56 (3.8)
Syncope	26 (1.8)

[a]Mild headache = self-resolving without medical intervention within 24 hours; moderate headache = lasting >24 hours; severe = requiring blood patch or hospitalization.

of dyslipidemia, cardiovascular disease, or prior LP complication, and normal Aβ_{42} levels. Complications were also associated with the use of a non-Sprotte (cutting needle) and the volume of CSF withdrawn. The mean difference in CSF volume between participants with and without a complication was <1 cc, and was deemed unlikely to be clinically relevant. Younger age, female sex, cognitively normal status, lower body mass index, and fewer years of operator experience were associated with severe complications (Table 3). When these variables were considered together via multivariable logistic regression, younger age, female sex, cognitive normal status, and use of a traumatic needle independently predicted an increased odds of a post-LP complication ($n = 1360$). Younger age, lower body mass index [BMI], and fewer years of clinician experience performing LPs were independent predictors of severe complications ($n = 1386$; Appendix A). In general, the multivariable model demonstrated a modest ability to identify participants who were likely to experience any complication (c-statistic, any complication = 0.65 [95% CI 0.61-0.68], $P < 0.001$), suggesting that unmeasured participant or procedural risk factors also influenced LP complications. By contrast, the model accurately identified participants likely to experience a severe complication (c-statistic, severe complication = 0.84 [95% CI 0.79-0.90], $P < 0.001$).

3.3 | Participation in serial lumbar punctures

Rates of participation in serial LPs among eligible participants declined following the first and second LPs before plateauing (Figure 1).

TABLE 3 Association between participant and procedural factors and post-LP complications

	Any complication, *n* = 331			Severe complication, *n* = 38		
Measured variables	Present	Absent	*P* value	Present	Absent	*P* value
Participant-specific factors at time of first LP						
Age, mean (±SD), years	65.8 (8.9)	69.2 (8.9)	**<0.001**	60.5 (9.7)	68.7 (8.9)	**<0.001**
Female sex, *n* (%)	218 (65.9)	610 (52.9)	**<0.001**	28 (73.7)	800 (55.3)	**0.02**
Education, mean (±SD), years	16.0 (2.4)	16.0 (2.7)	0.94	16.2 (2.4)	16.0 (2.6)	0.60
Non-Hispanic white, *n* (%)	298 (90.0)	1037 (89.9)	0.96	37 (97.3)	1298 (89.8)	0.17[a]
Cognitively normal, *n* (%)	294 (88.9)	919 (79.7)	**<0.001**	36 (94.7)	1177 (81.4)	**0.04**
Low CSF Aβ_{42}, *n* (%)	130 (39.4)	526 (46.1)	**0.03**	16 (42.1)	640 (44.6)	0.76
BMI, mean (±SD), kg/m^2	27.5 (5.9)	27.9 (5.4)	0.23	23.5 (3.3)	27.9 (5.5)	**<0.001**
APOEε*4* carrier, *n* (%)	112 (35.9)	427 (39.3)	0.27	15 (41.7)	524 (38.5)	0.70
Cardiovascular disease, *n* (%)	60 (18.1)	283 (24.5)	**0.02**	5 (13.2)	338 (23.4)	0.14
Cerebrovascular disease, *n* (%)[b]	11 (4.4)	42 (4.8)	0.81	2 (7.1)	51 (4.6)	0.38[a]
Dyslipidemia, *n* (%)	125 (40.1)	541 (51.1)	**0.001**	9 (32.0)	657 (48.9)	0.08
Diabetes, *n* (%)	32 (9.7)	98 (8.5)	0.51	0	130 (9.0)	0.07[a]
Hypertension, *n* (%)	137 (43.8)	485 (45.2)	0.66	9 (30.0)	613 (45.2)	0.10
Mood disorder, *n* (%)	70 (21.1)	223 (19.3)	0.47	4 (10.5)	289 (20.0)	0.15
Seizures, *n* (%)	6 (2.0)	27 (2.6)	0.55	1 (2.6)	32 (2.4)	0.61[a]
Smoking history, *n* (%)[b]	125 (47.9)	428 (44.9)	0.39	13 (38.2)	540 (45.8)	0.39
Thyroid disease, *n* (%)	51 (15.4)	203 (17.6)	0.35	6 (15.8)	248 (17.2)	0.83
Procedure-specific factors						
Operator experience, mean (±SD), years	4.5 (4.1)	4.4 (4.1)	0.56	2.6 (2.2)	4.4 (4.1)	**0.006**
Any prior LP complication, *n* (%)	331 (15.4)	124 (10.8)	**0.02**	1 (2.6)	174 (12.0)	0.12
Traumatic needle, *n* (%)	9 (2.7)	11 (1.0)	**0.03**[a]	0	20 (1.4)	>0.99[a]
Lateral decubitus position, *n* (%)	15 (4.5)	37 (3.2)	0.25	0	52 (3.6)	0.64[a]
Volume of CSF collected, mean (±SD), mL[b]	24.3 (2.6)	25.0 (2.3)	**0.001**	25.4 (2.5)	24.8 (2.4)	0.35

[a]Fisher exact test.
[b]Data missing for >10% of events.

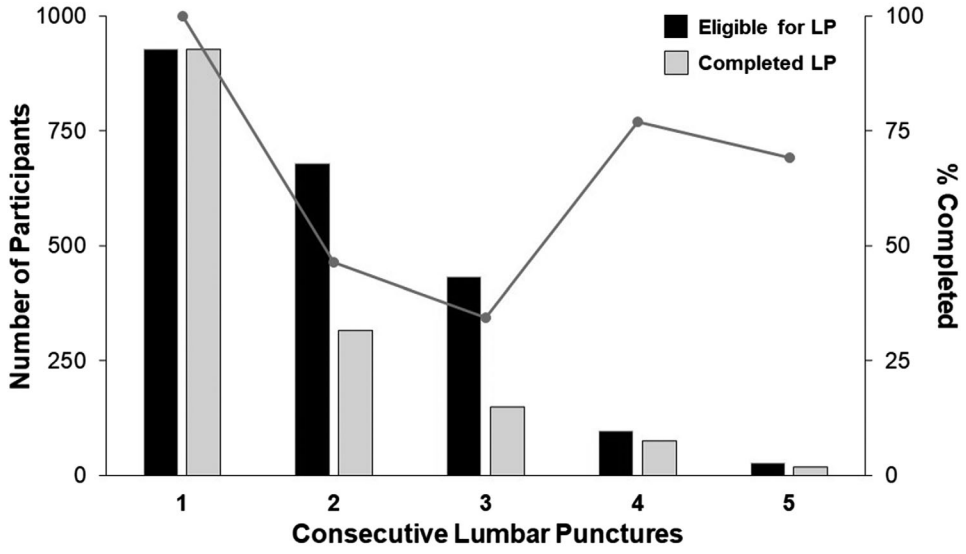

FIGURE 1 Rates of participation in serial lumbar punctures (LPs) at study entry and every 3 years thereafter. Participants eligible to complete serial LPs (black) are shown alongside of those who successfully completed serial LPs (gray). Rates of completion (solid line) demonstrate that participation rates declined from the first (study entry) to the third LP (year 6), before plateauing

The participant and procedural factors associated with serial LP completion are detailed in Table 4. Younger age, female sex, greater years of education, cognitively normal status, normal CSF Aβ_{42} levels, and the absence of cardiovascular disease, dyslipidemia, hypertension, or prior history of LP complication were overrepresented in participants completing two or more LPs. Similar factors were associated with completion of three or more LPs, with the exception of a history of dyslipidemia and prior LP complication (no longer associated) and seizures (now associated). Multivariable logistic regression established younger age, and cognitively normal status as independent predictors of serial completers (≥2 LPs; data from 678 eligible participants were included in the model). Unexpectedly, abnormally low CSF Aβ_{42} levels were also associated with greater odds of completing two or more LPs, when accounting for the effects of other variables, including cognitive status (Figure 2, Panel A). Young, cognitively normal participants without a prior history of heart disease exhibited the greatest odds of completing three or more LPs (data from 406 eligible participants were included in the model). No participants with a reported seizure disorder completed ≥3 LPs (Figure 2; Appendix B). Model statistics confirmed fair ability of the model to predict serial completion (c-statistic, ≥2 LPs = 0.79 [95% CI 0.76-0.83], $P < 0.001$; c-statistic, ≥3 LPs = 0.78 [95% CI 0.73-0.82], $P < 0.001$). Of interest, after controlling for the effect of other variables, a prior history of LP complication (including severe complication) did not deter participants from participating in serial LPs.

4 | DISCUSSION

Complications requiring medical intervention occurred following 2.6% of 1484 LPs performed in 929 older community-dwelling participants enrolled in longitudinal studies of memory and aging at our center. Younger age, lower BMI, and fewer years of clinician experience performing LPs were all associated with greater odds of a severe complication (namely, post-dural puncture headache). Other complications occurred following an additional 19.7% of LPs. Most of the complications were mild and self-resolving and did not influence odds of participation in a subsequent LP. Only younger age, normal cognition, and the absence of heart disease or history of seizure disorder at study entry increased the odds of participation in serial (≥3) LPs.

Rates and types of post-LP complications in community-dwelling volunteers in our studies were consistent with those reported in cohorts including patients for whom mild self-limiting side effects occurred following 11% to 30% of LPs, and more serious complications requiring intervention (eg, blood patch for post-dural puncture headache) were encountered in <5%.[15–20] Similar factors predisposing to post-LP complications were identified in the largest of these cohorts—a multi-center study performing LPs in 3456 unique patients at 23 European memory clinics.[17] Age <65 years, absence of a dementia diagnosis, and use of a traumatic (cutting) needle were also associated with increased risk of post-dural puncture headache in this multicenter study. Uniquely, this study also identified a prior history of headache, patient-expressed fears of post-LP complications, use of larger bore needle (<22 gauge), and upright positioning as key participant and procedural risk factors for moderate-to-severe post-dural puncture headaches.[17] Female sex was not associated with any increased risk of complications,[17] contrasting findings in this and other cohorts.[29,30] Taken together, this information can be leveraged to improve informed consent, providing individual participants with a realistic expectation of procedural risks. By identifying participants at the greatest risk of moderate-to-severe complications, it may also be possible to implement risk-reduction strategies, including the use of smaller gauge needles and lateral decubitus positioning in select individuals.[15,17,18]

TABLE 4 Association between participant and procedural factors and completion of serial LPs

	Eligible to complete ≥2 consecutive LPs ($n = 679$)			Eligible to complete ≥3 consecutive LPs ($n = 432$)		
Measured variables	**Completed**	**Not completed**	***P* value**	**Completed**	**Not completed**	***P* value**
Participant-specific factors at time of first LP						
Age, mean (±SD), years	65.3 (8.0)	72.0 (7.9)	**<0.001**	61.7 (8.6)	69.0 (9.3)	**<0.001**
Female sex, *n* (%)	184 (58.4)	178 (48.9)	**0.01**	78 (61.9)	143 (50.3)	**0.03**
Education, mean (±SD), years	16.2 (2.5)	15.6 (2.9)	**0.01**	16.1 (2.4)	15.7 (2.8)	0.15
Non-Hispanic white, *n* (%)	280 (88.9)	329 (90.4)	0.52	114 (90.5)	258 (90.8)	0.91
Cognitively normal, *n* (%)	300 (95.2)	224 (61.5)	**<0.001**	125 (99.2)	222 (78.2)	**<0.001**
Low CSF Aβ, *n* (%)	97 (30.9)	176 (48.4)	**<0.001**	31 (24.8)	112 (39.4)	**0.004**
BMI, mean (±SD), kg/m^2	27.9 (5.7)	27.3 (4.9)	0.14	28.0 (4.8)	27.7 (5.3)	0.60
APOEε*4* carrier, *n* (%)	106 (35.9)	144 (42.9)	0.08	41 (34.5)	99 (38.4)	0.46
Cardiovascular disease, *n* (%)	53 (16.8)	114 (0.31)	**<0.001**	14 (11.1)	70 (24.7)	**0.002**
Cerebrovascular disease, *n* (%)[b]	6 (2.3)	18 (5.6)	0.05	3 (3.2)	10 (4.1)	>0.99[a]
Dyslipidemia, *n* (%)[b]	103 (39.8)	165 (51.6)	**0.005**	40 (42.1)	117 (49.4)	0.23
Diabetes, *n* (%)	25 (7.9)	31 (8.5)	0.78	9 (7.1)	21 (7.4)	0.93
Hypertension, *n* (%)[b]	103 (39.3)	157 (47.9)	**0.04**	33 (34.4)	113 (46.1)	**0.049**
Mood disorder, *n* (%)	57 (18.1)	80 (22.0)	0.21	17 (13.5)	54 (19.0)	0.17
Seizures, *n* (%)	5 (1.6)	14 (3.9)	0.07	0	10 (3.6)	**0.03**
Smoking history, *n* (%)[b]	136 (43.9)	173 (48.7)	0.24	59 (46.8)	128 (46.7)	0.98
Thyroid disease, *n* (%)	46 (14.6)	49 (13.5)	0.69	19 (15.0)	38 (13.4)	0.65
Procedure-specific factors						
Any LP complication, *n* (%)	73 (23.2)	62 (17.0)	**0.046**	25 (19.8)	60 (21.1)	0.77
Severe LP complication, *n* (%)	11 (3.5)	11 (3.0)	0.73	6 (4.8)	13 (4.6)	0.94

[a]Fisher exact test.
[b]Data missing for >10% of events.

Clinician experience performing LPs was inversely correlated with the odds of severe LP complications in our study. This finding adds to a growing body of literature reporting positive correlations between clinician experience and patient confidence and operator stress and procedural complications,[31] and suggests that clinician experience (or lack thereof) may contribute to the wide variability in complication rates reported across studies.[15–20] Accordingly, clinician experience may represent an important modifiable procedural risk factor, raising the possibility that additional training aimed at reducing clinician stress and promoting familiarity with the procedure may reduce procedural complications while increasing participant confidence and comfort.

Standard procedures in our study included the use of a 22-gauge atraumatic needle in seated (upright) volunteers. These differences may have contributed to the higher incidence of complications requiring medical intervention in our cohort (2.6% [38/1484]) versus those reported in another large study (1.0% [33/3456][17]). However, this difference also may reflect the low threshold for offering and performing blood patch in volunteers in our study, owing to the ease of accessibility of blood patches at our center, history of excellent response in participants, and desire to minimize duration of symptoms in community-dwelling volunteers. Indeed, blood patches were performed in 38 of 41 (93%) of participants with post-LP headache lasting >24 hours in our study, but only 11 of 470 (2.3%) of patients in the Duit et al. cohort.[17] No participants in our study required hospitalization for management of post-LP complications (vs 23 [0.7%] patients[17]). It is unclear whether early use of autologous blood patches may mitigate symptom duration and the need for additional medical intervention or hospitalization.

Uniquely, this study identified independent predictors of participation in serial LPs, including younger age, absence of cardiovascular disease or seizure disorder, and normal cognition at study entry. Although the majority of these factors are associated with longevity, their selection was not attributable to a survival effect, noting that only participants who were eligible to complete a diagnostic LP were included in the longitudinal analyses (ie, participants who died, withdrew from the study, or developed an uncorrectable contraindication for LP[25] were excluded). Thus, it is more likely that advancing age, declining cognition, and the presence of comorbidities associated with frequent medication use (including antiplatelet agents) identified participants who were most likely to perceive LPs as burdensome. This information can be used to promote recruitment of individuals who are most likely to agree to longitudinal CSF sampling, while focusing retention efforts on participants who are at-risk of declining future LPs. Such efforts could include targeted educational campaigns emphasizing the importance of longitudinal biomarker measures in aging research (eg, see 32–34), in combination with practical initiatives aimed at reducing burden for aging cognitively impaired participants with increasing medical comorbidities.

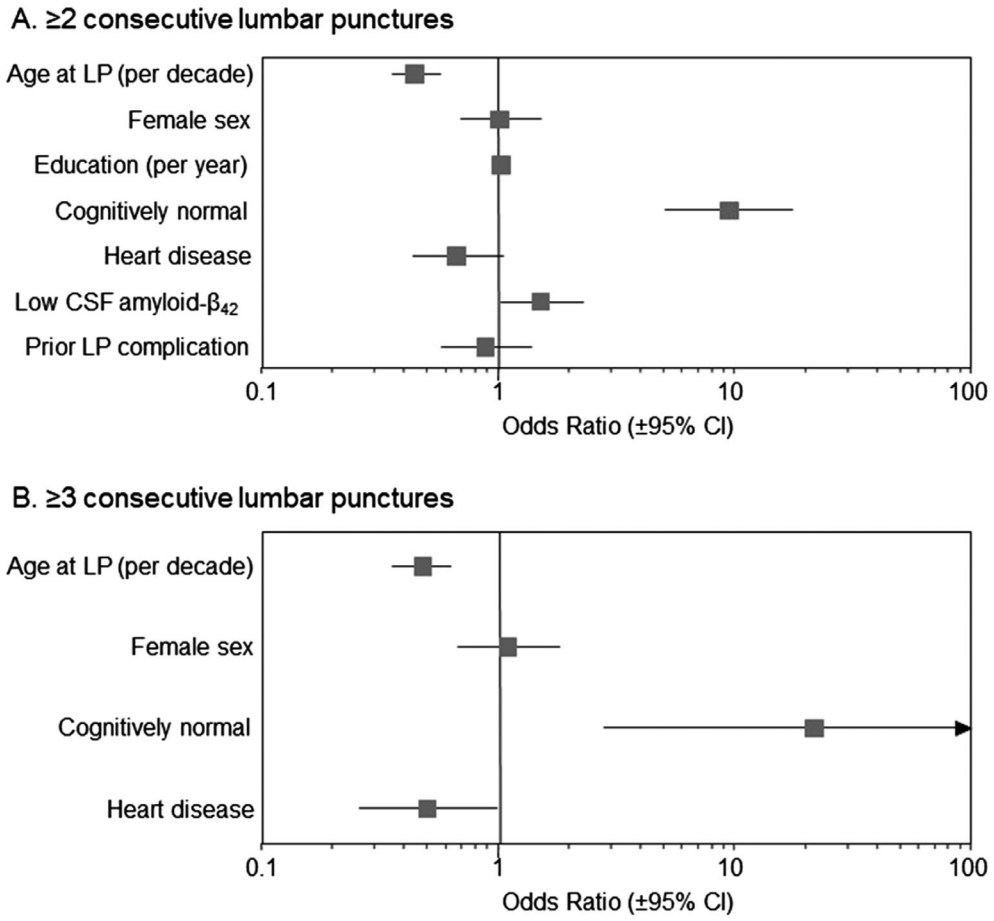

FIGURE 2 Factors influencing participation in serial lumbar punctures (LPs). Odds ratios ± 95% confidence intervals are shown for factors associated with participation in ≥2 (Panel A) and ≥3 consecutive LPs. No participant with a prior history of seizure disorder completed ≥3 LPs (OR ≈ 0; not shown)

This nested cohort study leveraged data from a large cohort of participants enrolled in studies of memory and aging at a single center. Although prospective collection of information is a strength, the parent studies were not designed to measure participant and procedural factors associated with participation in biomarker substudies. Accordingly, data were not available concerning several factors that may have influenced complications and longitudinal participation. Participant perceptions concerning LPs are one such factor, with participant anxiety and fear known to associate with complications and reticence to participate in LPs.[15,17,18,20] In addition, it is unknown whether rapid access to blood patches—a unique feature of this study—influenced participation in serial LPs. Reassurance of access to blood patches for the treatment of post-dural puncture headaches may represent one means of assuaging participant concerns regarding diagnostic LPs, although we acknowledge that the expertise and resources required to support this initiative may not be readily transferable to other research and clinical centers. As interest in and applications of longitudinal biomarkers continues to expand, it will become increasingly important to understand and protect against factors that increase LP complications and compromise participation in research incorporating serial CSF sampling, including both observational and clinical/therapeutic studies.

5 | CONCLUSIONS

Younger, cognitively normal participants without known heart disease or seizure disorder at study entry were more likely to participate in studies requiring serial CSF sampling. Prior history of LP complications did not influence participation in LP studies when controlling for the effect of other variables. Knowledge of the participant and procedural specific factors that influence participation in studies requiring serial CSF sampling may be leveraged to promote recruitment and retention within studies requiring serial LPs.

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AUTHOR CONTRIBUTIONS

G.S.D. participated in study design; acquisition and interpretation of data; statistical analysis; and drafting, revision, and finalization of the manuscript. T.R. participated in acquisition and interpretation of data, statistical analysis, and drafting of the manuscript. S.S. participated in acquisition of data, and revision and finalization of the manuscript. J.C.M. participated in acquisition and interpretation of data, and revision and finalization of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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