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Cognitive impairment and liver fibrosis in non-alcoholic fatty liver disease

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ABSTRACT

Background Data regarding the prevalence and phenotype of cognitive impairment in non-alcoholic fatty liver disease (NAFLD) are limited.

Objective We assessed the prevalence and nature of cognitive deficits in people with NAFLD and assessed whether liver fibrosis, an important determinant of outcomes in NAFLD, is associated with worse cognitive performance.

Methods We performed a prospective cross-sectional study. Patients with NAFLD underwent liver fibrosis assessment with transient elastography and the following assessments: Cognitive Change Index, Eight-Item Informant Interview to Differentiate Aging and Dementia Questionnaire (AD8), Montreal Cognitive Assessment (MoCA), EncephalApp minimal hepatic encephalopathy test and a limited National Institutes of Health Toolbox battery (Flanker Inhibitory Control and Attention Test, Pattern Comparison Test and Auditory Verbal Learning Test). We used multiple linear regression models to examine the association between liver fibrosis and cognitive measures while adjusting for relevant covariates.

Results We included 69 participants with mean age 50.4 years (SD 14.4); 62% were women. The median liver stiffness was 5.0 kilopascals (IQR 4.0–6.9), and 25% had liver fibrosis (≥7.0 kilopascals). Cognitive deficits were common in people with NAFLD; 41% had subjective cognitive impairment, 13% had an AD8 >2, 32% had MoCA <26 and 12% had encephalopathy detected on the EncephalApp test. In adjusted models, people with liver fibrosis had modestly worse performance only on the Flanker Inhibitory Control and Attention Task (β=−0.3; 95% CI −0.6 to −0.1).

Conclusion Cognitive deficits are common in people with NAFLD, among whom liver fibrosis was modestly associated with worse inhibitory control and attention.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Non-alcoholic fatty liver disease is associated with cognitive impairment and dementia.

WHAT THIS STUDY ADDS

⇒ This study adds granular phenotypical data regarding the nature and frequency of cognitive symptoms and deficits in people with non-alcoholic fatty liver disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study may prompt clinicians to consider cognitive screening/testing in patients with non-alcoholic fatty liver disease. Given the study limitations, however, more research on the liver–brain axis is required before other clinical practice changes would be justified.

INTRODUCTION

There is growing appreciation of the multiplicity of pathogenic factors underlying cognitive impairment,[1] and recognition that medical comorbidities may have important contributions to Alzheimer's disease and related dementias.[2] A greater understanding of the liver–brain axis will afford more comprehensive knowledge of the impact of systemic factors on brain health, which may in turn offer opportunities for targeting preventive interventions. Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease worldwide, impacting up to a quarter of the population.[3] While several studies have demonstrated an association between NAFLD and cognitive impairment and dementia, the data are conflicting as some studies reported either no association or a decreased risk of cognitive impairment in NAFLD.[4–11] For instance, an analysis from the Rotterdam study reported that NAFLD was protective against incident dementia in the first 5 years of follow-up.[12] However, the authors posited that rather than having a true protective effect against dementia, NAFLD simply reflects the absence of weight loss, which has been shown in several dementia cohorts to occur in the years preceding dementia onset.[13] Liver fibrosis is a condition that develops in up to 30% of people with NAFLD and reflects fibroinflammatory changes in the liver parenchyma rather than steatosis alone. In contrast to NAFLD, there are several consistent reports demonstrating the significance of liver fibrosis for cognitive and brain health.[14–18] Although there is a growing body of literature on the liver–brain

axis, data regarding the prevalence and granular phenotype of cognitive impairment in NAFLD remain limited. Additionally, many prior studies of NAFLD and cognition have not investigated the role of liver fibrosis in the relationship. Therefore, we conducted a prospective study to assess the prevalence and nature of cognitive deficits in people with NAFLD using a detailed battery of complementary cognitive assessments. We also aimed to test the hypothesis that liver fibrosis, as measured by liver transient elastography, is associated with cognitive impairment severity in people with NAFLD.

MATERIALS AND METHODS

Study design

We performed a prospective cross-sectional study embedded in the Innovative Center for Health and Nutrition in Gastroenterology (ICHANGE) Programme. The ICHANGE Programme is a multidisciplinary care model developed to treat people with NAFLD.[19] Participants are self-referred or referred to the ICHANGE Programme by their primary care doctors and other clinicians. The ICHANGE Programme cares for adults aged ≥18 with a body mass index (BMI) >25 kg/m^2 with NAFLD. The ICHANGE Programme excludes people with chronic liver disease from other causes, including viral hepatitis, alcoholic liver disease (based on report of >14 drinks/week for women and >21 drinks/week for men) and biliary disease. All participants referred to the ICHANGE Programme undergo liver fibrosis assessments using liver transient elastography. Additionally, participants undergo detailed cardiometabolic risk factor assessments. Participants then receive multidisciplinary care for long-term NAFLD management. For the purposes of this study regarding cognition, we prospectively recruited participants from the ICHANGE Programme for cognitive assessments from July 2020 to March 2022. Participants in ICHANGE provided written informed consent. The deidentified data that support the findings of this study and analytical methods will be made available to qualified investigators upon reasonable request.

Study population

The ICHANGE Programme excludes people with non-NAFLD causes of liver disease. For this study on NAFLD and cognition, we had the following reasons for exclusion: clinically overt cirrhosis (because cirrhosis is known to cause encephalopathy), neurodevelopmental disorders and circumstances precluding valid use of our cognitive tests (language barriers, significant visual impairment, significant hearing impairment). Informants were not required as patients seeking care for NAFLD are typically unaccompanied.

Assessment of liver fibrosis

For the assessment of liver fibrosis, each participant underwent liver transient elastography using the FibroScan (EchoSens, Paris) device using standard clinical procedures.[20] This is a well-validated, non-invasive, ultrasound-based technique for the assessment of liver stiffness, which reflects liver fibrosis.[21] The test estimates the degree of liver fibrosis based on the liver stiffness measurement by delivering a 50-hertz mechanical impulse and measuring the velocity of the generated shear wave.[22] It has been validated to have area under the curve values of 0.8–>0.9 for different stages of liver fibrosis.[21 23] For our analysis, we dichotomised participants based on liver stiffness using a sensitive cut-off (≥7 vs <7 kilopascals) because several studies have shown that this cut-off has a good area under the receiver operator curve (0.78) for fibrosis stage ≥2, and this cut-off corresponded to the top quartile in our study population.[24 25] For interpretation of our findings throughout this manuscript, 'liver fibrosis' in analyses of liver stiffness as a dichotomous variable should be taken to mean 'possible liver fibrosis of stage 2 or greater'. Given the varying cut-offs used in the literature for liver fibrosis,[26] we additionally evaluated liver stiffness as a continuous measure.

Assessment of cognition

Each participant underwent standardised screening tests and cognitive assessments using both pen-and-paper testing and tablet computer-based testing. Tests were selected in collaboration with a neuropsychologist (AJ). Each participant completed assessments in a private, quiet examination room with a trained research assistant. Evaluations were completed in the following order: Cognitive Change Index (CCI), Eight-Item Informant Interview to Differentiate Aging and Dementia Questionnaire (AD8), Montreal Cognitive Assessment (MoCA), EncephalApp and an abbreviated National Institutes of Health (NIH) Toolbox Cognition Battery.

The CCI is a cognitive assessment tool used to gauge subjective cognitive deterioration in memory, executive function and language.[27] Among the two CCI questionnaires, we used the subject-facing form. Subjects answer 20 questions on a scale of 1–5, with higher scores denoting a greater degree of cognitive deterioration.[27] The AD8 is a cognitive screening instrument used to assess changes in memory, problem-solving skills, orientation and daily functioning brought on by cognitive decline.[28] The AD8 requires participants to answer eight yes-or-no questions, with two or more positive responses indicating cognitive impairment.[28] The AD8 is sensitive for identifying Alzheimer's disease.[28] The MoCA test is included in the Uniform Data Set from the National Alzheimer's Coordinating Center.[29] The total score, ranging from 0 to 30, reflects global cognitive performance and was calculated by summing the scores from each task with an adjustment for educational attainment.[30] The EncephalApp, a smartphone-based Stroop test, is a neuropsychological test used to assess cognitive flexibility and psychomotor speed.[31 32] The Stroop test consists of two components—the Stroop effect Off State and the Stroop effect On State.[33] The EncephalApp has been validated for the screening of hepatic encephalopathy using primarily the

OffTime+OnTime; a cut-off of OffTime+OnTime >190 s identified participants with covert hepatic encephalopathy with 89.1% sensitivity and 82.1% specificity.[31]

The following NIH Toolbox tests were administered to assess complementary cognitive domains: Flanker Inhibitory Control and Attention Test (executive function), Pattern Comparison Processing Speed Test (processing speed) and Auditory Verbal Learning Test (episodic memory), in this order. The Flanker Inhibitory Control and Attention Test assesses attention and inhibitory control in 20 trials. During each 3-minute trial, participants are asked to focus on one stimulus while ignoring 'flankers', or distracting stimuli on the sides of the main stimulus.[34] We used the Pattern Comparison Processing Speed Test to assess processing speed and mental agility by asking participants to rapidly discern repeatedly whether two images were identical over 90 s.[35] In the Auditory Verbal Learning Test, participants are scored based on their ability to recall as many words as possible after listening to an audio-recording of 15 unrelated words.[36] The validity of the NIH Toolbox Cognition Battery has previously been demonstrated.[37] To report group-level summary data on these tests, we categorised participants as having mild-moderate impairment if the performance score was 'below average' (standardised score 70–79; 2nd–8th percentile) or 'exceptionally low' (standardised score <70; <2nd percentile) scores, as per consensus classification guidance.[38] We did this for the Flanker Inhibitory Control and Attention Test and the Pattern Comparison Processing Speed Test. However, the NIH Toolbox does not generate standardised scores for the Auditory Verbal Learning Test, so raw scores were reported.

Covariates

Demographic variables were age, gender, race, ethnicity (Hispanic vs non-Hispanic) and educational attainment. Race and ethnicity were both self-reported. Educational attainment was categorised as ≤12th grade education, some college, college completion and more than college completion. Hypertension was defined as self-reported diagnosis, blood pressure >140/90 mm Hg or use of antihypertensive medications; diabetes mellitus was defined as self-reported diagnosis or use of insulin or oral diabetes medications; dyslipidaemia was defined as total serum cholesterol ≥240 mg/dL or use of cholesterol-lowering medications. Additional covariates tabulated were BMI, history of tobacco smoking and alcohol use frequency. Smoking was defined as ever smoker versus never smoker. The number of standard alcoholic drinks per week was self-reported, and categorised as zero to one drink per

Table 1 Study participant characteristics, stratified by liver fibrosis*

	Total cohort n=69	Liver fibrosis n=17	No liver fibrosis n=52	P value†
Age, years	50 (14)	51 (17)	50 (14)	0.90
Women	43 (62%)	8 (47%)	35 (67%)	0.16
Race				
Asian	13 (19%)	4 (24%)	9 (18%)	0.52
Black	2 (3%)	0 (0%)	2 (4%)	
Other	17 (25%)	6 (35%)	11 (22%)	
White	35 (52%)	7 (41%)	28 (56%)	
Hispanic ethnicity	23 (34%)	5 (29%)	18 (36%)	0.77
Education				
Completed high school	7 (10%)	2 (12%)	5 (10%)	0.77
Some college	8 (12%)	1 (6%)	7 (14%)	
Completed college	26 (38%)	8 (47%)	18 (35%)	
More than college	27 (40%)	6 (35%)	21 (41%)	
Hypertension	37 (54%)	9 (53%)	28 (54%)	1.00
Dyslipidaemia	43 (62%)	11 (65%)	32 (62%)	1.00
Diabetes	13 (19%)	6 (35%)	7 (13%)	0.07
Body mass index	33 (5)	35 (6)	32 (5)	0.06
History of tobacco use	20 (29%)	5 (29%)	15 (29%)	1.00
Alcohol use				
0–1 drink/week	51 (75%)	13 (76%)	38 (75%)	0.88
2–7 drinks/week	14 (21%)	4 (24%)	10 (20%)	
>7 drinks/week	3 (4%)	0 (0%)	3 (6%)	

*Data are presented as n (%) or mean (SD), with liver fibrosis defined as >7 kilopascals on liver transient elastography.
†For comparison of values for liver fibrosis versus no liver fibrosis, Fisher's exact test for categorical variables and t-test for continuous variables were used.

week, two to seven drinks per week, and seven or more drinks per week (the study population excluded women with >14 drinks/week, men with >21 drinks/week).

Statistical analyses

Standard descriptive statistics were used to summarise data, reporting proportions, means (SD) and medians (IQR) as appropriate. We used Fisher's exact test and t-tests to compare continuous and categorical data for participants with versus without liver fibrosis. We used multiple linear regression models to examine the association between liver fibrosis, using liver stiffness first as a categorical variable (liver fibrosis vs no liver fibrosis) and then as a continuous variable, and cognitive outcome measures. Model 1 was unadjusted. Model 2 was adjusted for demographics, educational attainment and covariates that meaningfully differed among participants with versus without liver fibrosis ($p<0.20$), which were diabetes and BMI. The threshold of statistical significance was set at $\alpha=0.05$. Analyses were performed using SAS V.9.4.

RESULTS

Among 71 eligible participants, we included 69 after excluding 2 with invalid or missing liver fibrosis data. Overall, the mean age was 50.4 years (SD 14.4); 62% were women. Hypertension, diabetes and dyslipidaemia were prevalent in 37 (54%), 13 (19%) and 43 (62%) participants, respectively (table 1). The mean BMI was 32.6 (SD 5.4). The median liver stiffness was 5.0 (IQR 4.0–6.9), and 17 (25%) had liver fibrosis, defined as >7.0 kilopascals on liver elastography.

Overall, subjective and objective cognitive impairments were common (table 2). Based on the CCI, 28 (41%) had subjective cognitive impairment. Additionally, based on the AD8, nine (13%) had evidence of cognitive impairment with a score of >2. This was corroborated on the MoCA, for which 22 (32%) had a score of <26. The EncephalApp test detected evidence of encephalopathy in eight (12%) participants. Mild-moderate impairment based on age-standardised scores was seen in 17 (24%) participants on the Flanker Inhibitory Control and Attention Test and 9 (13%) participants on the Pattern Comparison Processing Speed Test.

We then assessed whether liver fibrosis was associated with worse scores on cognitive assessment tests (table 3). In adjusted models, people with liver fibrosis did not have worse scores on screening tests: CCI (β=1.5; 95% CI −4.8, 7.8), AD8 (β=0.8; 95% CI −0.1, 1.7), MoCA (β=−0.8; 95% CI −2.4, 0.7) and EncephalApp hepatic encephalopathy test (β=−1.5; 95% CI −23.6, 20.7). With regard to the NIH Toolbox Cognition Battery, liver fibrosis was associated with modestly worse performance on the Flanker Inhibitory Control and Attention Task (β=−0.3; 95% CI −0.6 to −0.1), but not with performance on the Pattern Comparison Processing Speed Test (β=−0.6; 95% CI −5.4, 4.2) or the Auditory Verbal Learning Test (β=0.3; 95% CI −3.0, 3.6). When using liver fibrosis as a continuous measure, similar results were seen except for the association of liver fibrosis with performance on the Flanker Inhibitory Control and Attention Task, for which a similar direction of effect was seen without statistical significance (β=−0.04; 95% CI −0.08, 0.003 for each 1-kilopascal increase in liver stiffness) (table 3).

Table 2 Cognitive screening and test scores

	Score*	N (%) with a positive test
Cognitive Change Index	23 (21–30)	28 (41)
The Eight-Item Informant Interview to Differentiate Aging and Dementia	0 (0–1)	9 (13)
Montreal Cognitive Assessment	27 (25–28)	22 (32)
EncephalApp OffTime+OnTime, s, mean (SD)	150 (43)	8 (12)
Flanker Inhibitory Control and Attention Test, mean (SD)†	92 (16)	17 (24)
Pattern Comparison Processing Speed Test, mean (SD)†	106 (20)	9 (13)
Auditory Verbal Learning Test, mean (SD)‡	23 (6)	–

*Scores presented as median (IQR) unless stated otherwise.
†Age-corrected standardised scores (mean 100) report for Flanker Inhibitory Control and Attention Test and Pattern Comparison Processing Speed Test. Participants were categorised as having a 'positive' test if they had mild-moderate impairment on test performance (standardised score <79, corresponding to ≤8th percentile).
‡Raw score presented for Auditory Verbal Learning Test; participants were not categorised based on this test.

DISCUSSION

In this single-centre, prospective, cross-sectional analysis, cognitive symptoms and deficits were common in patients with NAFLD, ranging from 12% to 41% depending on the measure used. Additionally, approximately 25% of patients with NAFLD had transient elastography evidence of possible liver fibrosis stage 2 or greater, which was modestly associated with worse performance on the Flanker Inhibitory Control and Attention Task, an executive function test of inhibitory control and attention.

Evaluating the epidemiological link between NAFLD and risk of cognitive impairment and dementia is challenging due to issues of confounding by shared risk factors.[8 12 13] There is growing, although conflicting, evidence that NAFLD independently increases the risk of cognitive impairment and dementia.[8 10 12] Our study builds on these data by systematically assessing the frequency and nature of cognitive symptoms and deficits specifically in this population, and further by evaluating the impact of liver fibrosis on these outcomes. Our findings suggest that patients with NAFLD have

Table 3 Association* of liver fibrosis with performance on cognitive tests

	Liver fibrosis vs no liver fibrosis	Liver fibrosis as a continuous variable
CCI		
Unadjusted	2.4 (–3.5, 8.2)	0.4 (–0.5, 1.2)
Adjusted†	1.5 (–4.8, 7.8)	0.5 (–0.7, 1.2)
Adjusted, standardised‡	0.1 (–0.5, 0.7); p=0.64	0.02 (–0.07, 0.11); p=0.63
AD8		
Unadjusted	0.6 (–0.2, 1.4)	0.1 (–0.1, 0.2)
Adjusted†	0.8 (–0.1, 1.7)	0.1 (–0.02, 0.2)
Adjusted, standardised‡	0.6 (–0.04, 1.2); p=0.07	0.1 (–0.02, 0.2); p=0.12
MoCA		
Unadjusted	–0.9 (–2.7, 1.0)	0.0 (–0.3, 0.3)
Adjusted†	–0.8 (–2.4, 0.7)	–0.1 (–0.3, 0.2)
Adjusted, standardised‡	–0.3 (–0.7, 0.2); p=0.29	–0.02 (–0.09, 0.05); p=0.61
EncephalApp		
Unadjusted	4.6 (–19.4, 28.7)	0.3 (–3.2, 3.8)
Adjusted†	–1.5 (–23.6, 20.7)	0.3 (–3.1, 3.6)
Adjusted, standardised‡	–0.03 (–0.6, 0.5); p=0.89	0.01 (–0.07, 0.08); p=0.87
Flanker Inhibitory Control and Attention Test		
Unadjusted	–0.3 (–0.6, –0.1)	–0.03 (–0.06, 0.004)
Adjusted†	–0.3 (–0.6, –0.09)	–0.04 (0.08, 0.003)
Adjusted, standardised‡	–0.8 (–1.4, –0.2); p=0.01	–0.09 (–0.18, 0.01); p=0.07
Auditory Verbal Learning Test		
Unadjusted	–0.0 (–3.1, 3.1)	0.07 (–0.4, 0.5)
Adjusted†	0.3 (–3.0, 3.6)	0.2 (–0.3, 0.7)
Adjusted, standardised‡	0.05 (–0.5, 0.6); p=0.86	0.03 (–0.06, 0.12); p=0.47
Pattern Comparison Processing Speed Test		
Unadjusted	–0.2 (–4.9, 4.5)	0.1 (–0.5, 0.8)
Adjusted†	–0.6 (–5.4, 4.2)	–0.0 (–0.7, 0.7)
Adjusted, standardised‡	–0.07 (–0.7, 0.5); p=0.80	–0.002 (–0.09, 0.09); p=0.97

*Association reported as β (95% CI).
†Adjusted for age, gender, race, ethnicity (Hispanic vs not), educational attainment, diabetes and body mass index.
‡For these adjusted models, the continuous outcome variable was standardised (mean=0, SD=1). In models of liver fibrosis as a dichotomous variable, the β corresponds to change in standardised outcome for fibrosis versus no fibrosis. In models of liver fibrosis as a continuous measure, the β corresponds to a change in standardised outcome for each 1.0-unit increase in liver stiffness.
AD8, Eight-Item Informant Interview to Differentiate Aging and Dementia Questionnaire; CCI, Cognitive Change Index; MoCA, Montreal Cognitive Assessment.

prevalence of subjective cognitive complaints as well as objective impairments in global cognition, executive function and processing speed. Approximately 12% had encephalopathy detected on the EncephalApp test, raising the possibility that cognitive impairments of some patients with NAFLD are in part due to a process akin to covert hepatic encephalopathy, a condition typically described in the setting of cirrhosis. Alternatively, given the hepatic encephalopathy is usually felt to be a late finding in advanced cirrhosis, it is possible that this finding instead reflects other types of deficits. For example, Stroop test deficits may be a marker for early-stage Alzheimer's disease.[39] Notably, we excluded patients with diagnoses of cirrhosis. Despite this, 25% of the cohort had possible subclinical liver fibrosis of stage 2 or greater, and the presence of such liver fibrosis was modestly associated with worse performance on a test of executive function, but not other tests. Acknowledging that the association of liver fibrosis with executive dysfunction was modest and the only statistically significant finding among several outcomes, our results suggest that liver fibrosis may contribute to executive dysfunction seen in NAFLD,[6 7 40] a pattern that has been identified at the population level as well.[14–18] However, executive dysfunction may predispose to unhealthy lifestyle behaviours that predispose to liver fibrosis; the

possibility of a bidirectional, non-causal association cannot be excluded.

While there are many outstanding questions regarding the role of liver disorders in cognitive impairment and dementia, the available data have two implications. First, screening for cognitive symptoms and deficits in patients with NAFLD may be informative. Conversely, future work should evaluate the utility of screening for NAFLD and liver fibrosis in patients with otherwise unexplained cognitive symptoms and deficits. Second, a growing literature justifies investigating whether liver-targeted treatments, such as lifestyle interventions to reverse NAFLD, or pharmacotherapy for liver fibrosis, have a role in the prevention and treatment of cognitive impairment.

Our work has several strengths, including filling a gap in the literature on the liver–brain axis by providing a comprehensive assessment of cognitive deficits in people with NAFLD. The use of a detailed battery of cognitive tests targeting different cognitive domains, including tests for the liver-specific condition of covert hepatic encephalopathy, allowed for a thorough investigation of cognitive impairment in this population. Additionally, our study adds to the small number of studies investigating the role of liver fibrosis in the link between NAFLD and cognitive impairment. However, there are several limitations that future work should seek to overcome. First, the relatively small sample size may have limited our ability to detect significant associations between liver fibrosis and cognitive outcomes, particularly for the MoCA and AD8, which have a restricted range of values. Relatedly, the overall distribution of liver stiffness indicates this was a relatively healthy study population with largely low-stage liver fibrosis, further limiting the ability to detect associations. Second, the cross-sectional design precluded an assessment of temporality or change in cognition over time. Third, our study was conducted in a single centre, which may limit the generalisability of our findings. Fourth, the lack of non-NAFLD controls limits inferences about whether the cognitive deficits seen in our NAFLD population are greater than would be expected in a population with similar age and comorbidities.

In conclusion, our study highlighted the prevalence of cognitive deficits in a single-centre cohort of people with NAFLD and highlighted the potential role of liver fibrosis in the relationship between NAFLD and cognitive impairment. Further research should comprehensively explore the complex relationship between NAFLD and cognitive impairment, including specifically with regard to the role of liver fibrosis.

Contributors Conceptualisation—NSP and SK. Methodology—NSP, SK and AJ. Formal analysis and investigation—NSP, SK and AJ. Writing (original draft preparation)—FW and NSP. Writing (review and editing)—CT, MI, VL, HK, SK and CI. Funding acquisition—NSP. Resources—NSP and SK. Supervision—CI. All authors contributed to the article and approved the final manuscript. NSP takes responsibility for the overall content as the guarantor.

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Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Weill Cornell Medicine Institutional Review Board (1810019707). Participants gave informed consent to participate in the study before taking part.

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Data availability statement The deidentified data that support the findings of this study will be made available to qualified investigators upon reasonable request.

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