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Glycated hemoglobin levels and geriatric depression impact cognitive status in an Indian urban elderly community

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ABSTRACT

This study explored the cognitive status of community-dwelling Indian older adults. Our objective was to observe the association of age-related cognitive change with other physiological health parameters like, glycated hemoglobin (HbA1c), and vitamin B12 in older adults in India. Urban community dwelling, consenting older adults (55–85years, n = 123), with no clinical history of cognitive or neurological problems participated in the study. The participants underwent a detailed demographic documentation and cognitive assessment comprising of tests from different cognitive domains and blood-based assessment of glycated hemoglobin (HbA1c) and vitamin B12. As expected, performance in all cognitive domains declined with increasing age. HbA1c levels correlated inversely with processing speed and executive function. Vitamin B12 levels did not correlate with performance on any cognitive test. Interestingly, geriatric depression correlated inversely with visuospatial abilities. A step-wise multiple regression revealed that HbA1c and geriatric depression contributed to 28 % variance on Montreal Cognitive Assessment while age did not qualify as a significant contributor. Using Petersen's criteria, Mild Cognitive Impairment (MCI) was observed in 17 % of participants. Participants classified as MCI had higher levels of HbA1c and geriatric depression, and lower performance in all cognitive domains compared to non-MCI participants. In conclusion, although cognitive performance declined with age, HbA1c and geriatric depression had a greater role in cognitive decline than age. With a high incidence of diabetes in India, this study highlights the prevalence of metabolism-linked changes in cognition, which are often ignored in community dwelling older adults in India.

Introduction

It is well established that cognitive changes are a normal aspect of ageing. However, understanding the pattern of cognitive change and associated risk factors in aging individuals are important to distinguish typical aging from impaired aging. When cognition declines beyond an acceptable range it affects quality of life, and importantly, it may be a sign of a neurodegenerative condition. With a growing aging population, globally as well as in India, understanding aging-related changes in cognitive health and associated risk factors need to be understood in community dwelling individuals. This is important for early detection and prevention of age-related neurodegenerative conditions.

Status of age-related cognitive changes in India

There are numerous studies on aging related cognitive changes in the North American and European populations. In the Indian context, only a handful of studies have studied aging related changes in cognition (Das et al., 2006; Kahali et al., 2023; Mathuranath et al., 2007; Nigam and Kar, 2020, Tripathi et al., 2014; Tripathi and Tiwari, 2011). These studies observed a decline in cognition as age advanced and that education can play a protective role. However, the cognitive tests administered in these studies are screening level tests such as Montreal Cognitive Assessment (MoCA), Addenbrooke's Cognitive Exam (ACE), or Mini Mental State Exam (MMSE). While these tests are sensitive to detect dementia, they may not be sensitive to detect mild or early changes in cognition (Hugo and Ganguli, 2014). These studies do not provide an in-depth assessment of cognitive function which is necessary to confirm early changes in cognition (Petersen et al., 2004). A study that did detailed assessments using the COGNITO battery in healthy Indian older adults > = 45 observed that decline in cognition became apparent around age 75 (Kahali et al., 2023).

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Overall, most studies from the Indian context give a screening level status of cognitive function in the elderly. We need more studies with detailed cognitive assessments which also take into account associated health factors in the ageing Indian population.

Glycated hemoglobin and cognition

Elevated levels of glycated hemoglobin (HbA1c) have shown to result in cognitive decline in diverse populations, namely German (Binder et al., 2017), Arabic (Maan et al. 2021), Hispanic (Mimenza-Alvarado et al., 2020), and English (Zheng et al., 2018). Furthermore, a graded cognitive decline was observed with increasing HbA1c levels, which included prediabetics (Zheng et al., 2018). Despite a high prevalence of prediabetes and diabetes in the Indian aging population (Jana and Chattopadhyay, 2022), studies on Type-2 diabetes patients in India have mostly used MoCA to assess cognitive impairment (Chakraborty et al., 2021; Lalithambika et al., 2019). When performance on MoCA is poor, further detailed cognitive assessments in all domains are needed to confirm cognitive impairment (Petersen et al., 2004). Additionally, these studies did not include prediabetic participants in their analyses. Studies that include graded elevation in HbA1c, irrespective of diabetes diagnosis, are necessary to understand the early changes in cognition and its correlation with glucose homeostasis, especially in a highly prediabetic population like India. Elevated HbA1c-related deficits include impairment in executive function (Zheng et al., 2018), processing speed and working memory (meta-analysis, Mansur et al., 2018), episodic memory (Pappas et al., 2017), language, attention, and visuo-spatial abilities (Dyer et al., 2021), along with gray matter atrophy - a sign of accelerated aging (Antal et al., 2022).

Vitamin B12 and cognition

The role of vitamin B12 in modulating cognitive abilities is ambiguous. Some studies have shown that low vitamin B12 levels are associated with low cognitive scores (Moorthy et al., 2012; Morris et al., 2012; Nalder et al., 2021) and risk for Alzheimer's disease (Lauer et al., 2022). However, many studies have also reported absence of association between vitamin B12 and cognition (Agnew-Blais et al., 2015; Zhang et al., 2020; Doets et al., 2013). Outcomes of interventions with vitamin B12 supplementation in older adults are also mixed. A few vitamin B12 intervention studies showed improvement in cognitive performance, especially when cognitive scores were low on MMSE (Sashindran et al., 2022) or in participants with mild cognitive impairment (de Jager et al., 2012). Some studies observed that vitamin B12 supplemented with folic acid and vitamin B6 improved the serum homocysteine levels, which did not necessarily translate to improvements in cognitive performance (Cheng et al., 2016; Dangour et al., 2015; Zhang et al., 2017). Further, other studies found no association between vitamin B12 intervention and cognitive performance in normally aging adults (Doets et al., 2013; Hvas et al., 2004; Markun et al., 2021).

Vitamin B12 absorption is known to decline with age (Baik and Russell, 1999) and its deficiency is endemic in the Indian population (Malik and Trilok-Kumar, 2020). Therefore, there is a need to study its relationship with cognitive abilities in the Indian elderly.

Goal of the current study

Firstly, as the number of elderly in India is increasing, we sought to comprehensively profile the cognitive status in community dwelling older adults to document age-related decline and prevalence of mild neurocognitive disorder (American Psychiatric Association, 2022) also known as mild cognitive impairment (MCI). Secondly, we aimed to explore the link between broad range of HbA1c levels and changes in cognition in the community dwellers. Thirdly, we explored the association of Vitamin B12 on cognitive changes in the elderly. We included participants in an unbiased manner from the community to get a realistic and detailed picture of the cognitive changes associated with the chosen risk factors.

Materials and methods

Participants

This study was approved by the Institutional Ethics Committees (IEC) at the National Center for Biological Sciences (NCBS) and at the University of Transdisciplinary Health Sciences and Technology (TDU), both at Bengaluru, India. Participants were recruited through healthy aging awareness talks with a focus on cognitive health at elderly enrichment centers and citizen forums in Bengaluru. Participants were also recruited through snowball referrals (word of mouth). None of the participants had visited a clinician for any mental or cognitive health complaint. The participants themselves and their families considered them to be aging normally.

A total of 123 participants between 55 and 85 years completed this study between 2018 and 2022 (with a year's break during COVID). Participants were included if they had at least 10 years of school education and had basic English proficiency (read and communicate). Detailed health record and family history were taken. Participants were excluded if they had i) history of brain injury; ii) neurological or psychiatric illness; or iii) severe hearing or visual impairment. Details of participants are summarized in Table 1.

Cognitive assessments, questionnaires, and blood parameters

Interested participants were given a choice to visit the research center or have a researcher visit their home to administer the cognitive tests. All cognitive tests and questionnaires were administered in the paper-pencil format and were completely in 90–120 min.

Measures to profile MCI

Montreal Cognitive Assessment (MoCA) has been shown to be sensitive in differentiating MCI from cognitively healthy participants (Chapman et al., 2016; Nasreddine et al. 2005; Roalf et al. 2013; Trzepacz et al., 2015). From a total MoCA score of 30, a score above 26 is considered normal. It also accounts for less than 12 years of education by adding 1 point to the total score.

Activities of Daily Living (ADLQ) is a questionnaire filled by informants (spouse/adult children) (Johnson et al., 2004). It is sensitive to mild decline and measures functional abilities in 6 areas - self-care, household care, employment and recreation, shopping and money, travel, and communication. The scoring gives a gradation of impairment of functional abilities (mild 0–33 %, moderate 34–66 %, and severe > 67 %). ADLQ correlates inversely with MoCA (Durant et al., 2016). To include changes due to normal aging, only those individuals with less than 33 % impairment were included.

Quick Dementia Rating Scale (QDRS) comprises of 10 questions related to cognitive, behavioral, and functional abilities. The first six questions in the QDRS give the Clinical Dementia Rating (CDR) Scale equivalent score (Galvin, 2015). The informant has to compare the participant's past-present abilities. The key feature is the change in cognitive abilities. The total score ranges between 0 and 30. Participants with scores ≥ 5, indicative of early dementia, were excluded. This scale is shorter than CDR and efficient for screening community members for research purposes (Berman et al., 2017).

Spielberger's Trait Anxiety Inventory (STAI) is a 20-item scale to evaluate levels of anxiety generally experienced by an individual, with scores ranging between 20 and 80 (Spielberger, 1983). This was collected to screen high anxiety levels > 50 in an older Indian population.

Subjective Memory Complaint Questionnaire developed by Youn et al. (2009) was used. Participants responded "yes" or "no" to 14 questions

Table 1
Summary of participant demographics and cognitive performance by age-decade.

		55-65 years (Group1, G1)	66-75 years (Group2, G2)	76-85 years (Group3, G3)	Statistics[a]
Number of participants (N)		51	41	24	-
Age [Mean, SD]		59.80 (3.07)	70.61 (2.91)	80.54 (2.75)	p<.001, η^2=.9 G1<G2<G3 (p<.001)
Education (years) [Mean, SD]		16.83 (2.43)	16.34 (2.86)	15.71 (2.79)	n.s.
Male/Female		24/27	17/24	12/12	n.s.
Languages spoken	Monolingual	1 (2%)[$]	0	0	-
	Bilingual	2 (4%)	4 (10%)	2 (8%)	-
	Multilingual	48 (94%)	37 (90%)	22 (92%)	-
Employment status	Employed	30 (60%)	11 (27%)	4 (16%)	-
	Homemaker	4 (7%)	9 (22%)	4 (16%)	-
	Retired	17 (33%)	21 (51%)	16 (66%)	-
Physical activity (Exercise)	No exercise	5 (10%)	9 (22%)	5 (21%)	-
	Irregular exercise	6 (12%)	5 (12%)	1 (4%)	-
	Regular exercise	40 (78%)	27 (66%)	18 (75%)	-
Family history of neurodegenerative illness		12 (23%)	5 (12%)	5 (21%)	-
Health Status (reported by participants)	Diabetes	7 (14%)	3 (7%)	1 (4%)	-
	Hypertension	7 (14%)	15 (36%)	10 (42%)	-
	Diabetes + Hypertension	3 (6%)	5 (12%)	3 (12%)	-
Blood Tests	Vit B12 (pg/mL) [Mean, SD]	253.9 (150.5) (n=33)	328.7 (191.87) (n=16)	382.5 (22.44) (n=8)	n.s.
	HbA1c (%) [Mean, SD]	6.31 (1.78) (n=34)	6.57 (2.03) (n=17)	6.81 (1.34) (n=9)	n.s.
Subjective memory score	[Mean, SD]	2.94 (2.26)	2.83 (2.55)	2.96 (2.40)	n.s.
MoCA score	[Mean, SD]	26.77 (2.2)	26.63 (1.8)	24.77 (2.48)	p<.001, η^2=.12 G1, G2 > G3 (p<.01)
Activities of Daily Living	[Mean, SD]	3.97 (4.95)	4.51 (5.13)	10.87 (11.06)	p<.001, η^2=.16 G1<G3 (p=0.01)
Quick Dementia Rating Scale	[Mean, SD]	0.68 (0.88)	0.85 (0.95)	1.5 (1.21)	p<.01, η^2=.1 G2<G3 (p=.05)
Trait Anxiety	[Mean, SD]	32.24 (6.91)	34.24 (7.76)	32.09 (8.85)	n.s.
Geriatric Depression	[Mean, SD]	1.49 (1.61)	1.95 (1.8)	2.42 (2.68)	n.s.
Classified as MCI	N	7	6	7	-
Cognitive Tests					
Memory [Mean, SD]	Spatial object DR (16 items)	8.88 (2.32)	8.93 (2.32)	7.0 (2.41)	p<.01, η^2=.1 G1,G2>G3 (p<.01)
	Spatial displacement DR (cm)	7.92 (3.10)	8.98 (4.24)	12.79 (6.91)	p<.001, η^2=.15 G1<G3 (p<.01) G2<G3 (p=0.05)
	AVLT trial 5	11.71 (1.94)	11.39 (2.02)	10.74 (1.94)	n.s. (p=.15)
	AVLT learning rate trials to learn 80% words (12/15)	4.71 (1.22)	5 (1.07)	5.39 (0.94)	p=.05, η^2=.05 G1<G3 (p=.03)
	AVLT IR	9.73 (2.67)	10.02 (2.67)	8.3 (3.56)	n.s. (p=.063)
	AVLT DR	9.41 (2.83)	9.44 (2.49)	7.91 (3.06)	n.s. (p=.068)
	AVLT recognition [z(hit)-z(false alarm)]	-0.03 (1.35)	0.17 (1.35)	-.25 (1.47)	n.s. (p=.5)
	Story IR	15.38 (2.5)	14.88 (3.47)	13.36 (2.96)	p=.03, η^2=.06 G1>G3 (p=.03)
	Story DR	13.28 (2.97)	12.24 (3.87)	10.44 (3.99)	p=.01, η^2=.09 G1>G3 (p=.01)
	Theme IR	5.79 (1.51)	5.38 (0.94)	4.89 (1.2)	p=.02, η^2=.07 G1>G3 (p=.03)
	Theme DR	5.26 (0.83)	5.03 (1.25)	4.35 (1.43)	p=.01, η^2=.09 G1>G3 (p=.03)
	Visual IR	15.12 (1.47)	14.67 (2.07)	13.87 (1.79)	p=.02, η^2=.07 G1>G3 (p=.01)
	Visual DR	13.14 (3.0)	12.64 (3.32)	9.54 (4.44)	p<.001, η^2=.14 G1>G3 (p≤.01)
	Visual Recognition	3.3 (0.83)	3.15 (0.83)	2.7 (0.63)	p=0.01, η^2=.08 G1>G3 (p<.01) G2>G3 (p=.04)

(continued on next page)

Table 1 (*continued*)

Attention & Executive Function	Digit Symbol Substitution Test (DSST) (90 sec)	45.78 (11.44)	41.09 (9.53)	32.25 (8.12)	p<.001, η^2=.2 G1,G2>G3 (p<.001)
[Mean, SD]	Digit Span Forward	8.39 (2.71)	8.22 (2.21	7.67 (2.14)	n.s.
	Digit Span Backward	5.06 (2.46)	5.27 (2.27)	4.5 (1.84)	n.s.
	Digit Span Total	13.45 (4.57)	13.49 (4.06)	12.17 (3.52)	n.s.
	Trail A time (sec)	57.49 (17.28)	64.83 (30.0)	71.67 (24.12)	p=0.05, η^2=.05 G1<G3 (p=.03)
	Trail B time (sec)	73.0 (29.47)	98.0 (53.33)	125.25 (61.96)	p<.001, η^2=.16 G1<G3 (p<.01) G1<G2 (p=.02)
Visuospatial Function [Mean, SD]	4 block designs (max. 6)	5.22 (1.07)	4.66 (1.59)	4.46 (1.77)	n.s.
	4 block avg time (max.=60sec)	28.25 (9.98)	32.92 (12.18)	35.86 (8.57)	p=.01, η^2=.08 G1<G3 (p<.01)
	9 block designs (max. 6)	4.32 (1.58)	3.41 (1.76)	2.83 (1.37)	p<.001, η^2=.12 G1>G2 (p=.03) G1>G3 (p<.001)
	9 block avg time (max.=120sec)	74.41 (23.02)	86.88 (18.89)	94.17 (17.44)	p<.001, η^2=.13 G1<G2 (p=.02) G1<G3(p<.001)
	Clock score (max. 12)	10.02 (1.71)	9.72 (1.65)	9.63 (1.94)	n.s.
	Maze total time (sec)	176.92 (74.1)	196.49 (75.45)	245.91 (101.6)	p<.01, η^2=.1 G1<G3 (p=.01)
Verbal [Mean, SD]	Letter fluency (words in 1 min)	14.69 (4.54)	14.98 (4.01)	12.87 (3.81)	n.s.
	Category fluency (words in 1 min)	17.88 (4.28)	17.02 (4.19)	14.30 (3.76)	p<.01, η^2=.1 G1>G3 (p<.01) G2>G3 (p=.03)

[a]Differences between the three age groups were analyzed using ANOVA for continuous variables and Chi-Square for categorical variables. Games-Howell post-hoc test was used for unequal variance. IR-immediate recall, DR-delayed recall. n.s. – not significant. Shaded cells denote significant difference in that age group. [$]percentage of participants in the respective age category.

that cover everyday, spatial, global, and prospective memory. These questions helped to prod older adults to review themselves on different memory functions.

Geriatric Depression Scale (GDS) is a screening tool for depressive symptoms in older adults (Sheikh and Yesavage, 1986). It has 15 questions with a 'yes' or 'no' response. Participants have to rate their feelings over the past one week. Scores above 10 are indicative of depression (Greenberg, 2007).

Cognitive tests

Memory tests

Spatial Memory Test was developed by Smith and Milner (1981) to test memory for objects and their spatial locations. A set of 16 toy objects were randomly placed on a 60 cm x 60 cm sheet of paper before the participant came into the room. Toy objects were doll-sized and included everyday items (bowl, bucket, car, chair, computer, cup, dress, hairbrush, necklace, pot, scissors, shoes, spanner, spatula, telephone, umbrella). For encoding, participants had to name each toy object and estimate its price if it were a real item. Objects were then taken out of sight and kept aside for a 90 min interval that was filled by other cognitive tests. At the end of the interval, for recall, participants had to name as many objects as they could remember. Subsequently, participants were given all the objects and were instructed to place them in their original locations on the paper. The original and recalled spatial positions of the objects were photographed with a top view of the sheet and were overlaid to calculate the absolute displacement (cm) of each object using ImageJ, an open-source software for analyzing images.

Rey's Auditory Verbal Learning Test (AVLT) test comprised of 15 unrelated words (List A) that were read aloud, one word per second, followed by a free recall. This was repeated over 5 trials. Subsequently, another list of 15 unrelated words (List B) was read aloud followed by a free recall. List B was read only once and served as interference (distractor list), followed by free recall of List A words (immediate recall). List A was recalled again after 20–30 mins (delayed recall), followed by a recognition of List A words. The recognition test included words from List A, List B, 15 semantically related words to List A, and 15 phonetically related words to List A. The standardized difference between hits and false alarms was the recognition score.

Logical (Story) Test consisted of listening and remembering a short story. Two passages from the Wechsler Memory Scale-III (WMS-III INDIA; Wechsler and Gurappa, 2009) adapted for the Indian population were used. Each passage was read aloud slowly and clearly in a neutral tone followed by an immediate and delayed recall (20–30 min). Each passage included 25 facts (details) and 7 themes (gist). Participant recall was audio-recorded and scored later.

Visual Reproduction Test assessed visual memory. Four figures were taken from the Wechsler Memory Scale-III (WMS-III INDIA; Wechsler and Gurappa, 2009). Participants were given 10 s to observe each stimulus figure and then taken out of sight. Then a blank sheet of paper was given and participants were instructed to draw the observed figure (immediate recall). Delayed recall (20–30 mins) for all 4 figures was followed by a recognition test, which included the original figure and 5 slightly distorted versions shown together. The point-scoring format was taken from the Wechsler Memory Scale.

Attention and executive function

Digit Symbol Substitution Test measured information processing and motor speeds, taken from the Wechsler Adult Intelligence Scale—Fourth Edition (WAIS–IV; Wechsler, 2008a). Number-symbol pairs were presented on top of a sheet and numbers from 1 to 9 in random order were printed below in multiple rows. Below each number participants had to draw the corresponding symbol as quickly as they could. The total number of correctly drawn symbols within 90 s constituted the score.

Digit Span Test measured attention and working memory. Random sequences of numbers were read aloud at the rate of 1 digit per second. Participants had to listen carefully and repeat the numbers in the same order (forward span). The number of digits in the sequence increased serially. The listen-repeat protocol continued until participants made errors on two consecutive sequences. Subsequently, participants repeated another set of numbers in the reverse order (backward span). The total number of correctly repeated forward and backward sequences comprised the score.

Trail Making A&B Test had two parts - Trail A primarily reflects visuo-motor abilities while Trail B measures working memory and attention shifting. In Trail A, participants had to connect circles numbered 1–25 presented in random locations on a sheet of paper. In Trail B, participants had to alternate between numbers (1−12) and letters (A-K) while connecting the dots (1-A-2-B-3-C). Time taken to complete both trails was noted.

Visuospatial abilities

Block Design Test measured visuo-spatial abilities and was taken from the Weschler Memory Scale, 3rd Indian edition. Participants were shown abstract designs which had to be reconstructed by assembling red and white blocks. Each of the 4-block designs (n = 6) had to completed within 60 s and 9-block designs (n = 6) within 120 s. The time taken to assemble the designs correctly was noted.

Maze Test can identify deficits in route planning and foresight in older adults (Staplin et al., 2013). Two standard mazes (no. 12 and no. 14) were taken from the Porteus Tests (Porteus, 1933). The time taken to complete the mazes was noted.

Clock Orientation Test measured mental rotation and egocentric spatial processing (Coughlan et al. 2018). Participants had to imagine that they were standing in the center of a large clock. They were asked to point to the direction of different numbers while facing a particular number (e.g. when facing 12 where is 5). The orientation becomes increasingly difficult over 12 questions. Time taken to respond and accuracy was noted.

Verbal (Language) abilities

Letter Fluency assessed the ability to generate words starting from a given letter within one minute, excluding names of people and places.

Category Fluency included naming as many animals as possible within one minute.

Blood parameters

A phlebotomist visited the homes of consenting participants (n = 61) and collected the blood samples (2–3 h post-prandial). Samples were analyzed for glycated hemoglobin (HbA1c %) and vitamin B12 (pg/ml) by a certified pathology lab. Blood samples were collected within a week of cognitive testing.

Results

In this study, 123 individuals were recruited and screened. Data from 116 participants was included in the analysis. Three participants with QDRS ≥ 5 and four participants with geriatric depression score > 10 were excluded from the analysis (Fig. 1). Table 1 summarizes demographics of included participants.

Age and cognition

The effect of age on cognitive performance was observed using a one-way ANOVA and Games-Howell post-hoc test for unequal variances. Effects of age by decade on performance on all cognitive tests is summarized in Table 1, along with effect sizes. The 76–85 age group had significantly lower performance than 66–75 age group and 55–65 age group on many cognitive tests across all domains. There was no significant change in cognitive performance between the first two decades. Further, as expected, Pearson correlation revealed an inverse association of age and MoCA scores ($r = -.32$, $p < .001$) (Fig. 2A).

Classification for mild cognitive impairment (MCI)

Cognitive performance of participants with MoCA≥ 26 in the 3 age groups (55−65, 66−75, 76−85) was used as age-appropriate reference/cognitive norms to calculate the extent of cognitive impairment. MCI was determined using 4-point Petersen criteria, namely i) MoCA< 26; ii) reduction in performance by ≥ 1.5 normalized standard deviations (SD) on two or more tests in the same or multiple cognitive domains when compared to age-matched participants with MoCA ≥ 26; iii) daily living

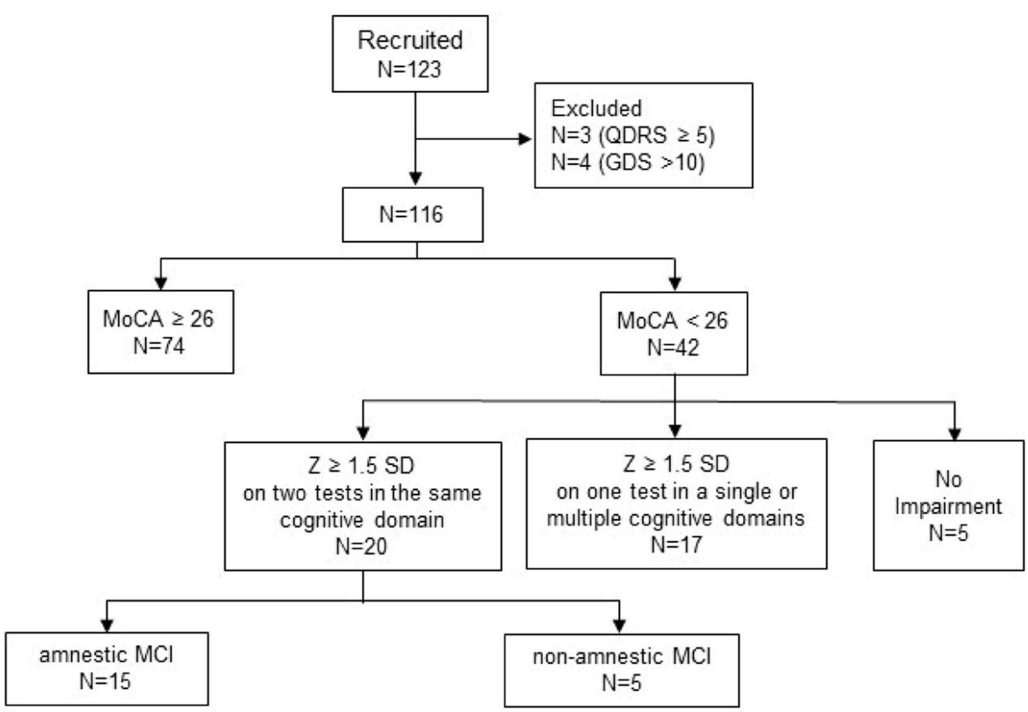

Fig. 1. Classification of participants based on MoCA into sub-types of MCI. Z = normalized standard deviation.

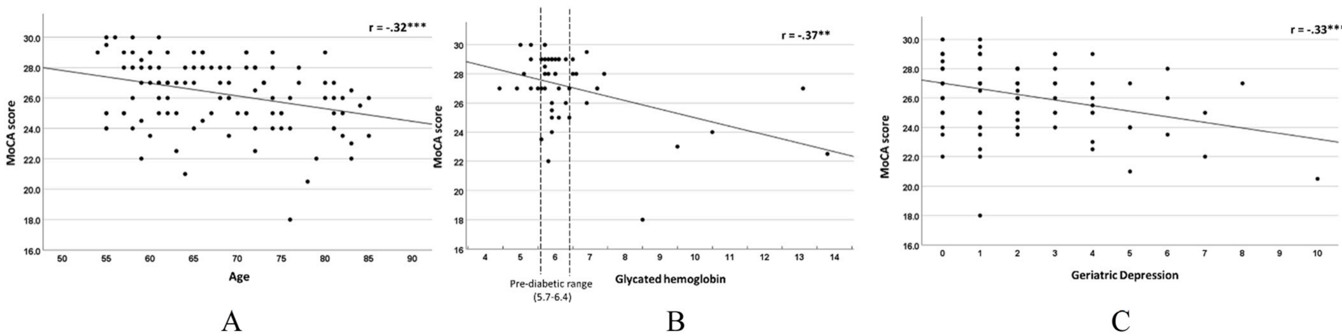

Fig. 2. Correlations of MoCA with A) age, B) glycated hemoglobin (HbA1c), and C) geriatric depression.

activities unaffected (ADLQ <33 %); iv) No dementia (QDRS < 5) (Sosa et al., 2012; Petersen, 2004). Subjective complaints were not included as a criterion to confirm MCI in this community dwelling cohort. Fig. 1 illustrates the classification of participants with MoCA< 26 in to sub-types of MCI. Participants with MoCA< 26 but no impairment (<1.5 SD on all cognitive tests) on any of the cognitive tests were considered non-impaired (Dautzenberg et al., 2020). Twenty participants (17 %) were classified as MCI. Multivariate Analysis of Variance (MANOVA) showed that performance on nearly all cognitive tests was lower in the MCI group compared to non-MCI group ($F_{(28,44)} = 6.27$, $p < .001$, Wilks' lambda $\Lambda = 0.2$, $\eta^2 = .8$) (Table 2).

Glycated hemoglobin (HbA1c) and cognition

Based on the HbA1c levels from 61 blood samples in our study, 24.5 % were non-diabetic (≤ 5.6 %, n = 15), 49.5 % were pre-diabetic (5.7–6.4 %, n = 30), and 26.2 % were diabetic (≥ 6.5&, n = 16). Of the participants who did not self-report and were not aware of their diabetic or pre-diabetic status, 14 % (n = 7/50) were in the diabetic range and 56 % (n = 28/50) were in prediabetic range, and only 30 % (n = 15/50) actually had normal blood glucose levels (HbA1c<5.6).

Pearson correlation revealed an inverse correlation of HbA1c and MoCA scores ($r = -.37$, $p = .004$). Interestingly, HbA1c correlated inversely with MoCA in the 55–65 yr group ($r = -.34$, $p = .047$) and 66–75 yr group ($r = -.53$, $p = .03$) even though HbA1c levels did not vary across the 3 age groups (Table 1). In addition, Fig. 2B shows that prediabetics also have scores < 26 on MoCA

HbA1c also correlated negatively on digit-pan forward ($r = -.3$, $p = .019$) and backward ($r = .32$, $p = .017$) and correlated positively with time taken to complete Trail A ($r = .28$, $p = .029$) and 4 block designs ($r = .3$, $p = .018$), all tests of executive function. Using a one-way ANOVA, we found that participants classified as MCI had higher HbA1c values compared to non-MCI participants ($F_{(1,49)} = 6.7$, $p = .012$, $\eta^2 = .12$) (Table 2); this analysis included all levels of HbA1c (including prediabetics). To assess whether high HbA1c levels affected different cognitive functions, as shown in previous studies with only diabetic population, HbA1c values were split into two groups, low level (<7 %, n = 50) and high level (≥7 %, n = 10). HbA1c = 7 %.was chosen to distinguish genuinely high values (typically seen in diabetics) and were analyzed using multivariate ANOVA to assess the effects on processing time and executive function as suggested by previous studies. An effect of high blood glucose ($F_{(8,51)} = 2.82$, $p = .05$, Wilks' Lambda $\Lambda = .8$, $\eta^2 = .2$) was observed. A Mann Whitney *U* test compared the low and high HbA1c groups and found significant differences in MoCA scores as well ($U = 119$, $p = .009$, $r = .34$). These effects are summarized in Fig. 3.

Vitamin B12 and cognition

Levels of vitamin B12 between 200 and 900 pg/ml are considered normal (Wolters et al., 2004). Participants were split in low vitamin B12 (<200, n = 25) and normal (≥200, n = 35) groups. Multivariate ANOVA did not show any difference between low and normal vitamin B12 groups on MoCA scores or any cognitive test. Pearson correlations between vitamin B12 level and individual cognitive test scores revealed no significant associations.

Geriatric depression and cognition

Pearson correlations revealed that geriatric depression scores correlated with MoCA scores ($r = -.33$, $p < .001$) (Fig. 2C) and tests of visuospatial function, such as average spatial displacement ($r = .23$, $p = .014$), visual delayed recall ($r = -.32$, $p < .001$), maze completion time ($r = .29$, $p = .002$), clock test ($r = -.25$, $p = .013$). Levels of geriatric depression were higher in MCI participants than non-MCI participants on a Mann Whitney *U* test ($U = 479$, $p = .013$, $r = .25$) (Table 2).

Regression of age, glycated hemoglobin, and geriatric depression on MoCA

From the results described above, Pearson correlation showed that MoCA scores were inversely associated with age ($r = -.31$, $p < .001$), glycated hemoglobin ($r = -.37$, $p = .003$), and geriatric depression ($r = -.33$, $p < .001$). A stepwise regression analysis was carried out to check the proportion of variance in MoCA contributed by these 3 factors. The regression analysis indicated that HbA1c ($\beta = -.41$, $p < .001$) and geriatric depression ($\beta = -.33$, $p = .004$) contributed significantly to 28 % of the variance in MoCA score (adjusted $R^2 = .28$, $F_{(2,60)} = 12.58$, $p < .001$) (Table 3). Age was not a significant contributor to the variance in MoCA. Semi-partial (part) correlations (r_{sp}), when squared, revealed unique contributions of geriatric depression (17 %) and glycated hemoglobin (11 %) to the 28 % variance in MOCA score (Fig. 4).

Discussion

With the ageing population increasing in India, understanding cognitive health and associated risk factors in the elderly is important. This study comprehensively profiled the cognitive status in community dwelling older adults across three decades (55–65, 66–75, 76–85 yrs) and also looked at the relationship of glycated hemoglobin, vitamin B12, and geriatric depression with cognitive abilities in older adults.

As expected, cognitive abilities gradually declined within the ageing cohort, with 76–85 yrs age group showing a significant decline. As glycated hemoglobin levels increased, speed of processing, executive function, and MoCA scores dropped. Vitamin B12 had no association with cognitive performance in our cohort. Surprisingly, geriatric depression was found to be associated with poorer visuospatial abilities and MoCA scores. Importantly, of the risk factors that correlated with MoCA, glycated hemoglobin and geriatric depression had a greater influence on MoCA performance, than age!

Table 2
Normal vs MCI differences in cognitive performance. *p < 0.05, **p < 0.01, ***p < 0.001.

		Normal (n = 74) MoCA≥ 26 Median (Q1, Q3)	MCI (n = 20) MoCA< 26 Median (Q1, Q3)	MANOVA effect size eta-squared (η^2)
	MOCA score	28 (27,29)	24 (22.6,24.7)	.67***
Memory	Spatial object DR	9 (7,11)	6.5 (5,8)	.18***
	Spatial displ. DR	8.05 (5.8,10.5)	8.8 (7.2,12.9)	n.s.
	AVLT Trial 5	12 (10.5, 13)	10 (9,10.7)	.13**
	AVLT learning rate	5 (4,6)	6 (5.2,6)	.08*
	AVLT IR	10 (8,12)	7 (5.2,9)	.14***
	AVLT DR	10 (8,11)	7 (5.2,9)	.09**
	AVLT Recog	.52 (−.5,1.2)	−.41 (−.2,.9)	.09**
	Story IR	16 (13.5,17.5)	13.2 (10.8,14.5)	.13**
	Story DR	13 (11,15.7)	9.75 (6.8,12.1)	.18***
	Theme IR	5.75 (5.2,6.2)	5 (4.2,5.5)	.05*
	Theme DR	5.5 (4.6,5.7)	4.1 (3.3,5.3)	.13**
	Visual IR	15.5 (14.5, 16)	13 (12,14.3)	.28***
	Visual DR	14 (12,15.5)	9.5 (6,12.1)	.23***
	Visual Recog	3 (3,4)	3 (2,3)	.11**
Attention & Executive Function	DSST	40.5 (35,52.2)	35.5 (32.5,40.7)	.07*
	Digit span forward	8 (7,10)	7 (6,8)	.07*
	Digit span backward	5 (4,7)	3.5 (1.2,5.7)	.10**
	Digit span total	14 (11,16)	10.5 (9,14)	.11**
	Trail A time	58 (45.7, 73.2)	67.5 (55.7,71.7)	.10**
	Trail B time	71 (52.7, 111.7)	76 (68,120)	.07*
Visuospatial Function	4 block designs	6 (4,6)	5 (3,6)	.08*
	4 block avg time/blk	26.67 (20.5,38)	39.6 (34.8,46.6)	.19***
	9 block designs	4 (3,5)	2 (1,4)	.14**
	9 block avg time/blk	78.8 (61.5,96.3)	106.2 (81,111)	.17***
	Clock score	10 (9,11)	10 (8.2,11)	n.s.
	Maze total time	159 (125,222)	249 (174,313)	.23***
Verbal	Letter fluency	15 (12.5,19)	12.5 (10,14)	.12**
	Category fluency	17 (15,21)	14 (12.2,16.7)	.19***
Other # (Mean, SD)	Geriatric Depression	1.4 (1.5)	2.7 (1.98)	.07*
	HbA1c	6.13 (1.31) (n = 39)	7.62 (2.66) (n = 11)	.12*

One-way ANOVA

Age related changes in cognition

Aging is known to alter cognitive function. As expected, we observed that with increasing age, MoCA (Fig. 2A) scores and performance in all cognitive domains gradually declined. Cognitive performance, however, was statistically different only between 55 and 65 yr and 76–85 yr groups on most cognitive tests (Table 1). This observation is in line with the earlier one that the decline becomes apparent around the age of 70 in the aging Indian population (Kahali, et al., 2023; Tripathi and Tiwari, 2011). Additional recent evidence suggests that sudden cellular and molecular decline occurs after the age of 70 that may translate to cognitive decline (Mitchell et al., 2022), which further supports our observations.

We briefly discuss performance on cognitive tests where effects of older age are not straightforward. Although delayed verbal recall (AVLT) gradually declined with age (Table 1), the difference across age decades did not reach statistical significance. Repetition over 5 trials of learning may have helped participants to retain words well compared to other memory tests, where participants are exposed to the stimuli only once. However, the rate of learning declined with age, participants took more trials to learn the words in AVLT as age increased (Table 1).

Letter fluency was unaffected by age while category fluency declined with age. Other studies have also noted such a dissociation and have shown that letter fluency may be affected by education rather than age, whereas category fluency may be affected by age (Tombaugh et al., 1999; Elgamal et al., 2011; Mathuranath et al., 2003). In this study education levels across decade-wise age groups were similar and therefore age may not have had an effect on letter fluency.

Forward or backward digit span performance did not change across the age groups. Since the study group consisted of only older adults, the effects on digit span across each decade of older life may be minimal. Similar null effects of age on digit span were reported in another study on Indian older adults (Tripathi et al., 2014) and in a Hispanic cohort (Pontón et al., 1996), where education correlated positively with digit span performance. Tripathi et al. (2019) have also reported a large effect of literacy on forward and backward span in an urban Indian cohort. Upon analyzing, we too found that years of education correlated positively with digit ***forward*** span performance ($r = .26$, $p = .005$), a small effect since the majority of our participants had higher levels of education.

We observed no effect of age on clock test performance. The clock test was designed to capture effects of aging on egocentric spatial processing (Coughlan et al., 2018). However, recent studies have shown that egocentric spatial processing is relatively less impaired in older adults compared to allocentric spatial processing (Colombo et al., 2017; McAvan et al., 2021).

Overall, a gradual decline in cognitive abilities in all domains was observed as age advanced, with noticeable differences post-70 years. Years of education played a protective role on tests of verbal fluency and digit span, where performance remained unaffected by across age-groups.

Glycated hemoglobin (HbA1c) was associated with processing speed and executive functions

Participants with higher levels of glycated hemoglobin had lower scores on MoCA. In fact, the decline was also visible in individuals in the pre-diabetic range (Fig. 2B). This highlights the fact that even before the manifestation of diagnostic level of diabetes, early dysregulation of glucose metabolism can lead to changes in cognition. Age-related decline in MoCA scores was observed only in the 76–85 group, yet, glycated hemoglobin-linked decline in MoCA scores was evident in 55–65 and 66–75 groups. Further, participants who were classified as MCI had higher levels of glycated hemoglobin. This suggests that cognitive function is connected to metabolic health, irrespective of age.

On tests of executive function, individuals with higher levels of glycated hemoglobin took longer to complete trail making and block design tasks indicating slower processing time, and were impaired on tests of digit span and digit symbol substitution (Fig. 3). These results align with observations in other cohorts (Mansur et al., 2018; Pappas et al., 2017; Zheng et al., 2018). Executive function and processing speed are dependent on the frontal regions that are typically affected by glucose dysregulation (Hishikawa et al., 2015; Weinstein et al., 2015). Performance on tests of memory, visuospatial abilities, and verbal fluency were unaffected by increase in levels of glycated hemoglobin. Others have also reported similar dissociations, where executive function and processing speed were affected by high glucose levels but

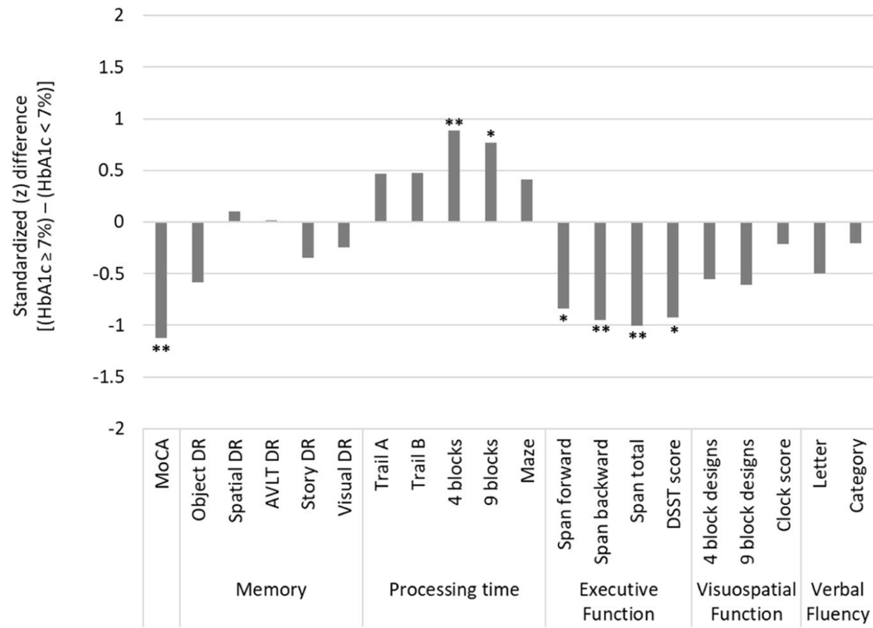

Fig. 3. Standardized (z) difference between participants with HbA1c $\geq 7\,\%$ (n = 10) and HbA1c $< 7\,\%$ (n = 50) in different domains of cognition. **p < 0.01, *p < 0.05.

Table 3
Multiple regression of age and HbA1c.

	B	95 % CI (B)	β	r_{sp}	r^2_{sp}	p-value	Adjusted R^2
Constant	30.62	[28.4, 32.78]					0.28
Geriatric Depression	−.48	[−0.74, −0.22]	−.41	−.41	0.17	< .001	
Glycated hemoglobin (HbA1c)	−.48	[−0.8, −0.16]	−.33	−.33	0.11	< .001	

B – unstandardized coefficient, β – standardized coefficient, r_{sp} – semi-partial correlation

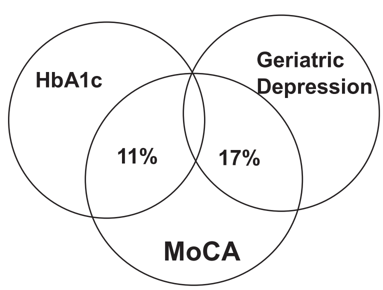

Fig. 4. Venn diagram of the variance in MoCA contributed by geriatric depression and HbA1c.

memory remained unaffected (Antal et al., 2022; Casagrande et al., 2021; Nandipati et al., 2012). Many of our participants were on anti-diabetic medication which has been observed to rescue memory impairments (Alagiakrishnan et al., 2013; Sritawan et al., 2021; Zhong et al., 2018). Such medication might have a role in protecting the decline in memory in our cohort also.

From a small community sample of 116, 61 participants consented to give blood samples, 15 were in the normal range (24.5 %) of glycated hemoglobin; 30 were in the prediabetic range (49.5 %), and 16 were in the diabetic range (26.2 %) of which only 9 participants were aware of their diabetes status. These numbers give a glimpse of the prevalence in urban community dwelling older adults who have begun to show changes in their cognitive abilities but are unaware of their metabolic health status. Although the number of participants in this analysis were low, it highlights an important link between metabolic and cognitive health. These findings need to be validated by future studies with higher number of prediabetics and diabetics.

Individuals with impaired glucose metabolism not only show decline in cognition but may also develop white matter hyperintensities (Hishikawa et al., 2015; Weinstein et al., 2015). Such vascular abnormalities are a risk for vascular dementia (Ott et al., 1996; Raffaitin et al., 2009; Vogelgsang et al., 2018). Community dwelling participants with higher levels of glycated hemoglobin, are thus, vulnerable to vascular dementia.

Prior studies on metabolism linked cognitive changes in the Indian population have reported changes primarily in MoCA scores in patients with clinically diagnosed Type-2 diabetes (Chakraborty et al., 2021; Lalithambika et al., 2019). Our attempt, through this study was to bring attention to the fact that prediabetics can also be vulnerable and leaving out prediabetics may give an incomplete picture of glucose metabolism linked cognitive changes.

Vitamin B12 had no association with cognition

There were no associations between vitamin B12 levels and MoCA scores or any other cognitive score. Similar outcomes have been noted in other studies (Agnew-Blais et al., 2015; Doets et al., 2013; Zhang et al., 2020). There appears to be a complex relationship between vitamin B12, other vitamins, and folic acid in regulating serum homocysteine levels. Folic acid regulates vitamin B12 levels, and when vitamin B12 levels drop, serum homocysteine levels go up which may lead to neurodegeneration (Morris et al., 2007). Most of our participants were in the normal but lower range of vitamin B12 and few participants who were taking oral vitamin B12 supplements had excessively high levels of vitamin B12. The effect of varying levels of vitamin B12 on cognition could not be observed.

Geriatric depression was associated with visuo-spatial abilities

Despite screening out individuals with high geriatric depression (Fig. 1), it had a negative association with performance on visuo-spatial tasks (spatial memory, delayed visual reproduction, maze completion time, clock score). Visuospatial tasks are dependent on the hippocampus, a region in the medial temporal lobe, whose function is modulated by cholinergic and serotonergic activity (Ridley et al., 1988). The activity of these neurotransmitters is sensitive to geriatric depressive modulation (Nobler et al., 1999) and may alter hippocampal activity (Gunning and Smith, 2011). Similar observations of late life depression affecting visuospatial performance have been reported in a Slovenian elderly population (Klojčnik et al., 2017).

Interestingly, the participants profiled as MCI had higher geriatric depression scores than non-MCI participants, in spite of excluding high geriatric depression scores from the analysis. Similarly, another study excluded clinically depressed older adults and yet found higher depression scores in the MCI group compared to controls on a hospital depression scale (Menon et al., 2020). These results suggest a contributory role of geriatric depression in impairing cognitive function in older adults (Mohan et al., 2019; Muhammad and Meher, 2021; Steffens and Potter, 2008), a novel finding, especially in the context of Indian community-dwelling older adults.

Limitations

This study has a relatively small sample to reflect community data. Secondly, most cognitive tests were in English, and regional translations were unavailable for all tests, therefore only older adults with basic proficiency in English were included. However, most participants (>90 %) were multilingual and therefore results from this study could be generalized to other multilingual, age and education matched, individuals.

Conclusions

Our study was an attempt to get an in-depth status of cognitive function in a general population of community dwelling older adults who had never visited a clinician for cognitive complaints. Within a cohort of older adults, age-related decline became prominent in the 70 s. The results highlighted the significance of metabolic and psychological health for healthy cognitive aging. Glycated hemoglobin and geriatric depression were observed to be more important for cognitive health, than age. Since, pre-diabetes and diabetes are very prevalent in many parts of the world, including India, these findings are relevant to current global health scenario.

Author contributions

BD and AG conceptualized the study. BD and AS administered the tests on participants. SH coordinated serum data collection. BD and AS analyzed the data. All authors wrote the manuscript.

CRediT authorship contribution statement

Bhaktee Dongaonkar: Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Arman Deep Singh:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Swathi B Hurakadli:** Resources, Methodology, Data curation. **Ashwini Godbole:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Compliance with ethical standards

The authors declare that this study complies with all relevant ethical guidelines, regulations, and policies, including those at our respective institutes and the IBRO journal. This information is also stated in the Methods section of the submitted manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Data Availability Statement

All data is summarized and tabulated in the manuscript. Raw data will be made available on request.

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