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Impact of scheduled water intake on mild cognitive impairment in patients with orthostatic hypotension

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Orthostatic blood pressure (BP) dysregulation can impair cerebral blood perfusion and cognition. Water intake prevents syncope caused by orthostatic hypotension (OHypo) and improves orthostatic tolerance. However, research on scheduled water intake's effect on the association between OHypo and cognition is limited. This study aimed to investigate the impact of scheduled water intake on orthostatic BP dysregulation and mild cognitive impairment (MCI). This cross-sectional study was conducted in rural Fuxin, Liaoning Province, China, using cohort data. Water intake patterns were self-reported, and orthostatic BP was measured. MCI was assessed with the Chinese version of the Montreal Cognitive Assessment-Basic (MoCA-BC).Latent class mixed models were applied to identify systolic BP trajectory patterns. Logistic regression was used to examine the association between orthostatic BP abnormality and MCI, adjusting for potential confounders and including an interaction term for orthostatic BP abnormality and water intake regularity. Linear regression was used to analyze the relationship between orthostatic BP abnormality and total MoCA-BC score. Subgroup analyses were conducted based on age and water intake regularity. The study included 1576 participants: 1236 (78.4%) had normal recovery, 234 (14.8%) had delayed recovery, 36 (2.3%) had OHypo, and 70 (4.5%) had orthostatic hypertension. The average age was 63.2 ± 7.7 years, with a daily water intake of 1612.5 ± 978.8 ml; 1055 (66.9%) were female. Unscheduled water intake significantly interacted with OHypo on MCI (OR 5.82; 95% CI 1.17–35.34; *P* = 0.039). After adjusting for confounders, scheduled water intake was associated with a lower OR of MCI in those with OHypo (OR 0.11; 95% CI 0.02–0.44; *P* = 0.003), while unscheduled water intake showed no significant association (OR 0.99; 95% CI 0.41–2.57; *P* = 0.985). Scheduled water intake is linked to a lower risk of MCI in individuals with OHypo, suggesting a protective role. Promoting scheduled water intake might be inversely associated with MCI in OHypo patients. Further longitudinal studies are needed to confirm these findings and understand the mechanisms involved.

Keywords Orthostatic hypotension, Mild cognitive impairment, Hydration, Water intake, Blood pressure

Orthostatic hypotension (OHypo) is a prevalent blood pressure(BP) regulation disorder, which is classically defined as a drop in systolic BP of at least 20 mmHg and/or a drop in diastolic BP of at least 10 mmHg within

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three minutes of standing or head-up tilt[1,2]. This pathological change can lead to insufficient cerebral perfusion, causing symptoms such as dizziness, vertigo, and, in some cases, cognitive impairment[3]. The symptoms are more frequent in women, and comorbid factors and the estrogen mechanisms may contribute to a less effective compensation for the drop in blood pressure in response to positional change among women[4]. The prevalence of OHypo increases with age, affecting approximately one in five community-dwelling adults over the age of 60 and one in four individuals in long-term care facilities[5]. The most common comorbidity among patients with OHypo is hypertension, which is present in approximately 70% of patients, due to the decrease in autonomic and baroreflex function[6]. Conversely, OHypo is present in about 10% of patients referred to hypertension specialists[7]. Additionally, up to a quarter of patients presenting with unexplained syncope and severe orthostatic intolerance are diagnosed with OHypo[8]. OHypo negatively affects quality of life, can lead to traumatic falls, shortens life expectancy, and increases the risk of various conditions, such as falls, coronary heart disease, and stroke, making it a significant public health concern [9–12].

Mild cognitive impairment (MCI) is a state between normal cognitive aging and dementia[13]. Emerging evidence suggests a potential association between OHypo and MCI, although current research findings are not yet consistent[14–18]. Meta-analyses in older adults showed that OHypo is associated with worse cognition expressed as lower Mini Mental State Examination (MMSE) scores[19,20]. Some studies have indicated that OHypo is a significant clinical factor in cognitive impairment[21,22]. The recurrent cerebral hypoperfusion caused by OHypo might contribute to cognitive decline by affecting the brain's structural and functional integrity[23,24].

Water is the only essential liquid nutrient and the physiological basis for body hydration[25]. Recent studies have found that, in addition to medication and posture adjustments, water intake may have a positive impact on managing OHypo[26,27]. Effective treatment of OHypo often requires a combination of drug therapy and non-pharmacological approaches, such as physical counter-manoeuvres and intermittent water-bolus treatment. Multiple randomized controlled trials have confirmed the practical benefits of water intake for OHypo treatment[28–30]. A recent meta-analysis assessed the effects of rapidly ingesting 350 to 500 mL of water on systolic and diastolic BP and heart rate (HR)[31]. The results indicated that rapid water intake can lead to short-term increases in both systolic and diastolic BP and a slight reduction in HR in OHypo patients while seated or supine. Healthy participants also exhibited similar, but milder, effects. Drinking water can increase blood volume, thereby improving cardiac output and stabilizing BP, which can potentially relieve OHypo symptoms[32]. Studies have indicated that the sympathetic activation induced by water ingestion can result in alterations in systemic vascular resistance. This effect tends to be more significant in older adults with age-related changes in baroreflex function or in patients suffering from severe baroreflex abnormalities caused by neurodegenerative diseases[33]. These findings support the role of water intake as a simple and effective strategy for managing OHypo.

However, despite this preliminary evidence, the impact of scheduled water intake on the cognitive status of OHypo patients remains largely unknown. Cognitive function is a crucial aspect of daily life, and its impairment can significantly affect an individual's quality of life and independence. Limited research exists on how long-term scheduled water intake affects the association between orthostatic BP dysregulation and cognition. If water intake, a convenient, cost-effective, and patient-friendly non-pharmacological intervention can improve cognitive function in OHypo patients and if a more effective water intake pattern can be identified, it could become a promising and widely applicable therapeutic strategy. Therefore, this study aims to investigate the regulatory effect of scheduled water intake on orthostatic BP dysregulation and MCI. Understanding this relationship could provide new insights into the management of OHypo and offer valuable guidance for developing more effective interventions to improve the quality of life and cognitive health of OHypo patients.

Methods

Study population

The data for this study were obtained from a longitudinal cohort conducted in rural areas of Fuxin Autonomous County, Liaoning Province, China[34]. This is a part of the chronic disease cohort study. To ensure sample representativeness, the research area was divided into three parts: eastern, southern, and northern. Based on demographic characteristics, two townships from the southern part, one from the northern part, and one from the eastern part were selected, respectively. Thirty-three villages were then chosen from these four townships based on geographic locations. A questionnaire survey of the general population was conducted from June 2021 to August 2021. Participants were considered eligible if they were 35 years of age or older, had stayed in the study area for at least five years, and were willing to sign a consent form. Exclusions were made for individuals who were pregnant, had severe liver or renal failure, or were unwilling to participate. Ultimately, 3482 participants completed this survey.

The present study used a cross-sectional design with the follow-up survey data in 2021. We excluded participants according to our prespecified criteria: (1) age under 50 years (n = 407); (2) without a valid orthostatic BP assessment (n = 939) ; (3) without a cognitive function evaluation (n = 254); (4) with central nervous system disorders and presence of stroke (n = 119); (5) missing data on other key variables (n = 155); (6) with abnormal value ($P_{97.5}$: > 5000 ml/day) of daily water intake (n = 26); and (7) without classification of orthostatic BP (n = 6). Finally, 1576 participants were included in the present analyses (sFigure 1).

Data on demographics and other factors, including demographic features, lifestyle, and history of disease were recorded by interview. This study was carried out in accordance with the Declaration of Helsinki and all the procedures adhered to the ethical standards of the responsible committee on human experimentation at China Medical University (No. [2018]083). Written informed consent was obtained from all participants involved in the study. For illiterate participants, written informed consent was obtained from their proxies.

Assessment of water intake pattern

The assessment of water intake patterns was conducted by asking participants a series of questions about their hydration habits. Specifically, participants were asked: "Do you have a regular habit of drinking water?" Using guide questions, we further inquired: "Do you drink water at scheduled times each day, or only when you feel thirsty?" To evaluate the volume of water intake, participants were asked: "How many milliliters of water do you drink each day?" To ensure the accuracy of water intake measurements, participants were provided with a 500 ml container as a reference when estimating their daily water consumption. These questions aimed to provide a comprehensive understanding of both the frequency and quantity of water consumption among the participants.

Assessment of orthostatic blood pressure

Orthostatic BP was evaluated through four consecutive BP measurements. The procedure was as follows:

1. Participants rested in a supine position on a flat, hard bed for 5 min, after which their supine BP was measured (baseline).
2. Participants then changed their posture to a standing position, and their BP was measured immediately (approximately 30 s after the orthostatic change).
3. After the participants rested for more than 1 min, their BP was measured again (1–3 min after the orthostatic change).
4. After the participants rested for more than 1 min again, their BP was measured once more (3 min after the orthostatic change).

BP was measured by trained investigators using uniformly calibrated automatic electronic sphygmomanometers (HEM-8102A), with an accuracy of 0.1 mmHg. Timing for the measurements was recorded using a stopwatch on a mobile phone, accurate to 0.1 s. The investigators were clinical professionals who received standardized training before the commencement of the survey. A dedicated supervisor was responsible for ensuring that the investigators adhered to the standard procedures throughout the measurement process.

Based on the changes in systolic BP between the supine and standing positions, participants were categorized into different groups as follows[1,2,35]:

1. Normal: The change in systolic BP within 20 mmHg from baseline for all three standing measurements (a threshold of 30 mmHg was used for patients with supine hypertension).
2. Delayed BP Recovery: Any of the first two standing BP measurements (within 3 min) showed a drop exceeding 20 mmHg, but the third measurement (after 3 min) was "normal".
3. OHypo: The third standing BP measurement (after 3 min) showed a drop exceeding 20 mmHg (a threshold of 30 mmHg was used for patients with supine hypertension).
4. Orthostatic Hypertension(OHyper): The second or third standing BP measurement showed an increase exceeding 20 mmHg.

Assessment of cognitive function

The Montreal Cognitive Assessment (MoCA), published in 2005, has been proven more sensitive and reliable in MCI screening than other scales[36]. For the present study, we used the Chinese version of the Montreal Cognitive Assessment-Basic (MoCA-BC) to assess cognitive function and identify MCI among rural Chinese adults with varying education levels. The MoCA-BC is a 30-point assessment that evaluates nine cognitive domains: executive function, episodic memory, orientation, calculation, abstraction, delayed recall, visuospatial skills, naming, and attention. Higher scores on this test indicate a greater level of overall cognitive function[37]. The optimal MoCA-BC cutoff scores used for MCI assessment were 19 for individuals with six or fewer years of education, 22 for those with 7–12 years of education, and 24 for those with more than 12 years of education[38]. The MOCA-BC scale was conducted by specially trained investigators.

Assessment of other variables

Data on demographic characteristics (age, sex, ethnicity and educational level), lifestyle factors (smoking, alcohol consumption, and physical labor level), history of disease (supine hypertension and diabetes), and medication history were collected by face-to-face interviews with a standardized questionnaire.

According to the WHO's 1997 definition of smoking status[39], this study categorized smoking status into three groups: "Non-smoking," "Former smoking," and "Current smoking." Individuals who had smoked at least one cigarette daily for a minimum of six months were considered smokers. Those who had quit smoking for over six months were classified as "Former smoking," while those who had not were categorized as "Current smoking." In alignment with the guidelines from "The Physicians' Guide to Helping Patients with Alcohol Problems," issued by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in 1995[40], alcohol consumption in this study was similarly categorized into "Non-drinking," "Former drinking," and "Current drinking." Drinkers were defined as those consuming at least three drinks per week for six months. Drinkers who had abstained for more than six months were classified as "Former drinking," whereas those who had not were labeled as "Current drinking." Physical labor was rated three levels, low, moderate and high, based on the physical activities participants engaged in. Hypertension was taken as an antihypertensive medication in the last 2 weeks, DBP ≥ 90 mmHg or SBP ≥ 140 mmHg[41]. Diabetes was characterized by a fasting serum glucose level of 7.0 mmol/L or higher, the use of hypoglycemic drugs or insulin, or a self-reported diagnosis of diabetes by a physician or other healthcare professionals[42]. Body mass index(BMI) was calculated as weight (kg)/height $(m)^2$ (kg/m^2). Blood samples were obtained and estimated glomerular filtration rate (eGFR) was calculated based on the CKD Epidemiology Collaboration (CKD-EPI) equation[43].

Statistical analysis

Continuous variables are represented by mean ± standard deviation (SD), while categorical variables are represented as percentages. Due to the asymmetrical distribution, MoCA-BC is described using the median (interquartile range, IQR). ANOVA, Kruskal–Wallis rank sum test, and χ^2 test were used to compare individual characteristics and medication history differences between the orthostatic BP abnormality groups.

The orthostatic BP dysregulation was categorized into four groups: normal recovery, delayed recovery, OHypo, and OHyper, with 6 uncategorized participants excluded. We used R software (version 4.1.1) with the lcmm package to construct latent class mixed models (LCMM), which modeled the trajectory of SBP based on measurement time points (see Supplementary Methods section). The model incorporated measurement time points, orthostatic BP abnormality and their interaction with measurement time points. The within-participant correlation was explained by the random intercept and slope of the measurement time points. Finally, we plotted the SBP trajectory by the specific orthostatic BP abnormality groups.

A Logistic regression model was used to analyze the association between orthostatic BP abnormality and MCI. The model adjusted for daily water intake, age, sex, BMI, eGFR, education level, ethnicity, smoking, alcohol consumption, physical labor level, medication (diuretics, α-adrenergic blockers, vasodilators), supine hypertension, diabetes, as well as the interaction term between orthostatic BP abnormality and regularity of water intake. The covariate selection was based on several factors: (1) demographics (age, sex, education level, ethnicity); (2) interest in this study (daily water intake); (3) factors believed to potentially influence the OHypo and MCI based on previous studies (BMI, eGFR, smoking, alcohol consumption, physical labor level, α-adrenergic blockers, vasodilators, supine hypertension, diabetes).

Interaction analysis uses a multiplicative model, which incorporates the product term of the interaction variable into the regression model. If the interaction term showed statistical significance, then we would display the impact of the interaction effect through a simple effect analysis. The results of the interaction analysis showed statistical significance, thus we conducted all regression analyses in scheduled and unscheduled water intake subgroups. We also used a linear regression model to analyze the association between orthostatic BP abnormality and the total MoCA-BC score. Furthermore, we performed subgroup analysis based on age, comparing participants aged 50–60 years and those aged 60 years and above.

Results

Characteristics of participants

As shown in Table 1, this study finally included 1576 participants, of whom 1236 (78.4%) had normal recovery, 234 (14.8%) had delayed recovery, 36 (2.3%) had OHypo, and 70 (4.5%) had OHyper. The average age of the participants was 63.2 ± 7.7 years, the average daily water intake was 1612.5 ± 978.8 ml, and 1055 (66.9%) of the participants were female. 1168 (74.1%) of the participants had unscheduled water intake, and 972 (61.7%) had MCI. There were differences in age, BMI, smoking status, physical labor level, MoCA-BC score, supine hypertension, and diabetes prevalence among participants with different orthostatic BP dysregulation. For the use of hypertension-related drugs (sTable 1), the use of any hypertension medication was associated with orthostatic BP dysregulation. Specifically, the use of diuretics, β-adrenergic blockers, and Chinese patent medicine was associated with orthostatic BP dysregulation. In sTable 2 and sTable 3 , we show the basic characteristics and drug use of cognitively normal and MCI participants, and the results show that age, sex, BMI, ethnicity, education level, smoking, and eGFR are associated with MCI. Furthermore, the basic characteristics based on gender and age comparisons are presented in sTable 4 and sTable 5.

Trajectories of orthostatic BP regulation

Figure 1 shows the trajectory of BP recovery after orthostatic change. The x-axis represents 4 times measurements, and the y-axis represents systolic BP. The different colored lines represent the groups of orthostatic BP abnormality, and the shaded area represents the 95% confidence interval. It can be seen that the normal group has a slight decrease in SBP 30 s after the orthostatic change and then recovers. The delayed BP recovery group has a significant decrease in SBP 30 s after the orthostatic change and then gradually recovers. The OHyper group has a significant decrease in SBP 30 s after the orthostatic change and then does not recover. Finally, the OHyper group has a SBP increase of 30 s after the orthostatic change and then continues to rise and approach a higher stable level. sTable 6 provides the interaction analysis results of the four trajectories of orthostatic BP abnormality, showing that there is a statistically significant effect of differences between all four curves ($P < 0.001$), and the two-way comparison also has statistical significance. Spaghetti plots of changes in SBP in these 4 groups was shown in sFigure 2.

Moderating effect of the regularity of water intake and orthostatic BP abnormality on MCI/cognitive score

We first described the prevalence of MCI among participants with different orthostatic BP abnormalities, categorized by regularity of water intake. The results are shown in Fig. 2, and the prevalence of MCI was lower in the group with scheduled water intake compared to the group with unscheduled water intake (27.27% vs. 68.00%, $P = 0.030$, $P_{for\ interaction} = 0.040$) among the OHypo participants. The results of the interaction analysis between regularity of water intake and orthostatic BP dysregulation on the MCI/cognitive score are shown in Tables 2 and 3. The interaction between unscheduled water intake and OHypo on the MCI is statistically significant (OR 5.82; 95% CI 1.17–35.34; $P_{\text{for interaction}} = 0.039$); the interaction between unscheduled water intake and OHypo on delayed recovery score is statistically significant ($\beta = -1.56$; 95% CI −3.12 to −0.004; $P_{\text{for interaction}} = 0.050$). After adjusting for confounding variables (Fig. 3), in participants with scheduled water intake, the ORs of MCI in those with delayed recovery, OHypo, and OHyper compared to normal recovery were 1.04 (95% CI 0.54–2.06; $P = 0.899$), 0.11 (95% CI 0.02–0.44; $P = 0.003$), and 5.94 (95% CI 1.28–44.85; $P = 0.040$),

	Overall, n = 1576	Normal recovery, n = 1236	Delayed recovery, n = 234	Orthostatic hypotension, n = 36	Orthostatic hypertension, n = 70	P[a]
Age, yrs	63.2 ± 7.7	62.8 ± 7.7	63.7 ± 8.0	63.7 ± 7.0	66.9 ± 6.9	< 0.001
BMI, kg/m^2	24.77 ± 3.39	24.82 ± 3.33	24.21 ± 3.50	24.49 ± 4.00	25.83 ± 3.33	0.003
Sex, female (%)	1055 (66.9)	829 (67.1)	149 (63.7)	24 (66.7)	53 (75.7)	0.311
Regularity of water intake, unscheduled (%)	1168 (74.1)	912 (73.8)	174 (74.4)	25 (69.4)	57 (81.4)	0.487
Water intake, ml/day	1612.5 ± 978.8	1609.1 ± 986.5	1664.9 ± 944.3	1620.8 ± 1094.3	1492.9 ± 898.9	0.630
Water intake						0.592
< 1000 ml/day	328 (20.8)	258 (20.9)	42 (17.9)	10 (27.8)	18 (25.7)	
1000–2000 ml/day	740 (47.0)	588 (47.6)	108 (46.2)	14 (38.9)	30 (42.9)	
≥ 2000 ml/day	508 (32.2)	390 (31.6)	84 (35.9)	12 (33.3)	22 (31.4)	
Ethnicity						0.076
Han	1024 (65.0)	785 (63.5)	165 (70.5)	26 (72.2)	48 (68.6)	
Mongolian	503 (31.9)	416 (33.7)	59 (25.2)	10 (27.8)	18 (25.7)	
Others	49 (3.1)	35 (2.8)	10 (4.3)	0 (0.0)	4 (5.7)	
Education						0.324
≤ Primary school	625 (39.7)	479 (38.8)	92 (39.3)	17 (47.2)	37 (52.9)	
Middle school	701 (44.5)	560 (45.3)	103 (44.0)	15 (41.7)	23 (32.9)	
≥ High School	250 (15.9)	197 (15.9)	39 (16.7)	4 (11.1)	10 (14.3)	
Smoking status						0.010
Non-smoking	1075 (68.2)	856 (69.3)	153 (65.4)	15 (41.7)	51 (72.9)	
Former smoking	387 (24.6)	300 (24.3)	58 (24.8)	15 (41.7)	14 (20.0)	
Current smoking	114 (7.2)	80 (6.5)	23 (9.8)	6 (16.7)	5 (7.1)	
Alcohol consumption						0.667
Non-drinking	1199 (76.1)	941 (76.1)	173 (73.9)	29 (80.6)	56 (80.0)	
Former drinking	304 (19.3)	240 (19.4)	50 (21.4)	5 (13.9)	9 (12.9)	
Current drinking	73 (4.6)	55 (4.4)	11 (4.7)	2 (5.6)	5 (7.1)	
Physical labor level						< 0.001
Low	412 (26.1)	300 (24.3)	62 (26.5)	13 (36.1)	37 (52.9)	
Moderate	850 (53.9)	692 (56.0)	118 (50.4)	16 (44.4)	24 (34.3)	
High	314 (19.9)	244 (19.7)	54 (23.1)	7 (19.4)	9 (12.9)	
MCI, yes (%)	972 (61.7)	747 (60.4)	154 (65.8)	20 (55.6)	51 (72.9)	0.080
MoCA-BC[b]	19.0 [15.0, 22.0]	19.0 [16.0, 22.0]	18.0 [15.0, 22.0]	19.0 [14.75, 22.25]	18.0 [13.25, 21.0]	0.024
Hypertension, yes (%)	866 (54.9)	667 (54.0)	129 (55.1)	22 (61.1)	48 (68.6)	0.098
SH, yes (%)	898 (57.0)	679 (54.9)	162 (69.2)	21 (58.3)	36 (51.4)	0.001
Diabetes, yes (%)	256 (16.2)	196 (15.9)	34 (14.5)	5 (13.9)	21 (30.0)	0.015
Dyslipidemia, yes (%)	446 (28.3)	342 (27.7)	69 (29.5)	12 (33.3)	23 (32.9)	0.666
CHD, yes (%)	205 (13.0)	158 (12.8)	32 (13.7)	3 (8.3)	12 (17.1)	0.593
eGFR, ml/min/1.73m^2	90.81 ± 11.16	91.06 ± 11.03	89.98 ± 11.80	91.24 ± 8.63	88.83 ± 12.19	0.243

Table 1. Demographic characteristics in overall participants and orthostatic BP abnormality groups. [a]ANOVA, Kruskal–Wallis rank sum test, and χ^2 test were used to compare individual characteristics, as appropriately; [b]MoCA-BC is described using the median [interquartile range, IQR]; BP, blood pressure; BMI, body mass index; MCI, mild cognitive impairment; MoCA-BC, the Chinese version of Montreal Cognitive Assessment-Basic; SH, supine hypertension; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate.

respectively; in participants with unscheduled water intake, the ORs of MCI in those with delayed recovery, OHypo, and OHyper compared to normal recovery were 1.30 (95% CI 0.90–1.89; $P = 0.171$), 0.99 (95% CI 0.41–2.57; $P = 0.985$), and 1.00 (95% CI 0.54–1.93; $P = 0.990$).

The linear regression analysis between orthostatic BP dysregulation and cognitive score in participants with unscheduled/scheduled water intake is shown in sFigure 3. There is no statistically significant association between OHypo and cognitive score ($\beta = -1.00$; 95% CI −2.71–0.72; $P = 0.255$) in participants with unscheduled water intake. However, OHypo is associated with a higher cognitive score ($\beta = 2.50$; 95% CI −0.02 to 5.02; $P = 0.052$) in participants with scheduled water intake. There is no statistically significant association between OHyper and cognitive score ($\beta = 0.08$; 95% CI −1.10 to 1.25; $P = 0.899$) in participants with scheduled water intake. However, OHyper is associated with a lower cognitive score ($\beta = -2.31$; 95% CI −4.66 to 0.03; $P = 0.053$) in participants with scheduled water intake. Subgroup analysis based on age was presented in sFigure 4 and sFigure 5.

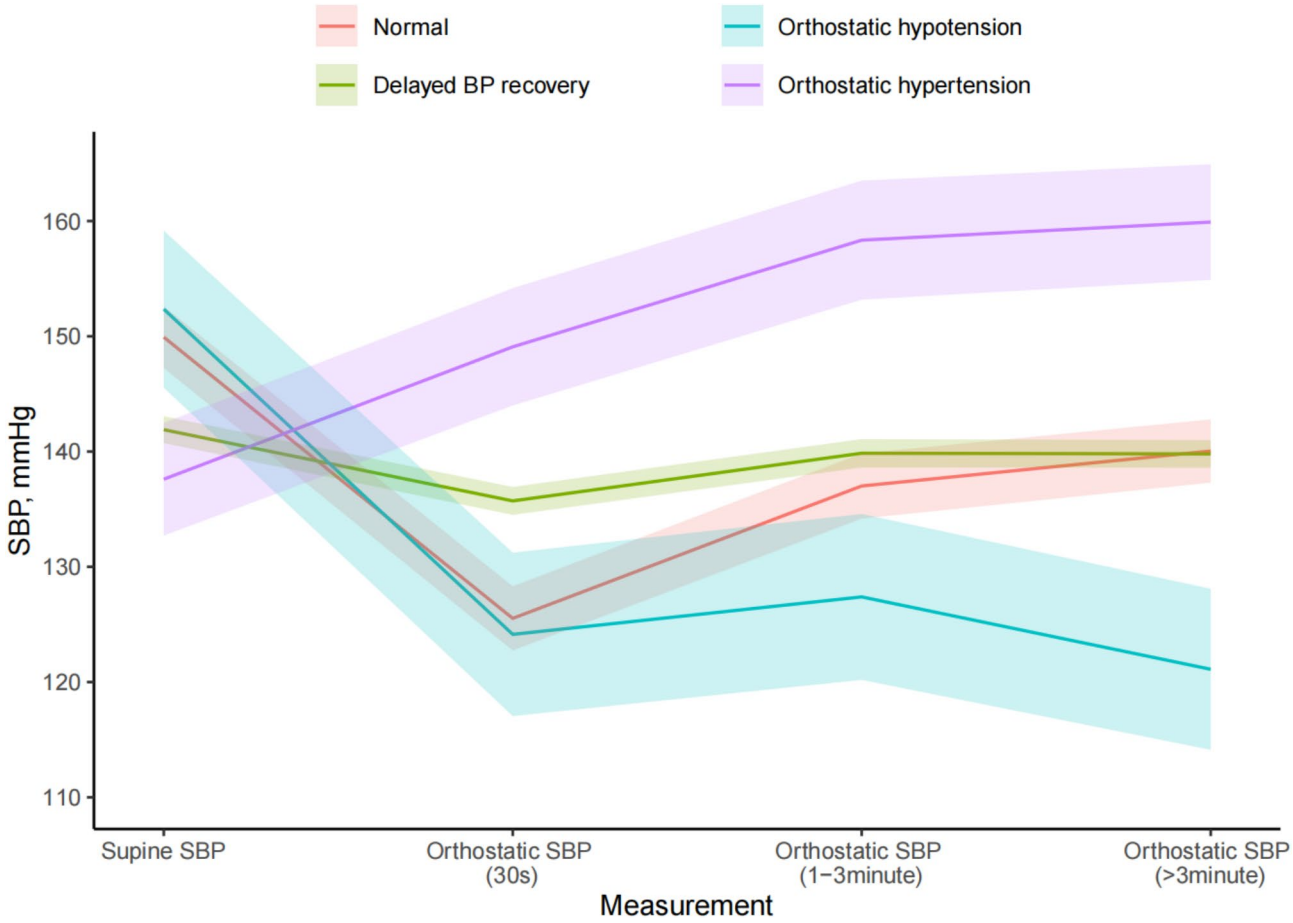

Fig. 1. Trajectory of SBP recovery after orthostatic change in the specific orthostatic BP dysregulation groups. Latent-class mixed models (LCMM) were used to model the trajectory of SBP according to measurement time points. The light-shaded portion is the 95% confidence interval for the SBP, which is calculated using Monte Carlo of the posterior distribution of the predicted values.

Discussion

The present study aimed to investigate the effects of scheduled water intake on orthostatic BP dysregulation and cognitive function among a rural Chinese population. A notable finding of this study is the moderating effect of scheduled water intake on the association between orthostatic BP dysregulation and MCI. Specifically, individuals with scheduled water intake exhibited a lower OR for MCI compared to those with unscheduled water intake, suggesting that scheduled and consistent hydration might play a protective role against cognitive decline in the context of OHypo.

According to current consensus criteria, OHypo is classically defined as a drop in SBP of at least 20 mmHg and/or a drop in DBP of at least 10 mmHg within three minutes of standing or head-up tilt. These criteria are widely accepted in clinical practice; however, the definition of OHypo applied in research settings has varied considerably. For example, a meta-analysis assessed the prevalence of OHypo in Parkinson's disease[44]. Notably, only five out of the 25 reviewed studies in this meta-analysis adhered strictly to the consensus criteria, highlighting the variability in diagnostic approaches in research contexts. Consistent application of diagnostic criteria is essential for accurate prevalence estimation and effective management. Wieling et al. have uncovered four major subtypes of OHypo via improvements in hemodynamic profiling with continuous BP measurements: initial OHypo, delayed blood pressure recovery, classic OHypo, and delayed OHypo[1]. In our study, we based our classification on the work of Wieling et al. and current consensus criteria, dividing our participants into four categories: normal recovery, delayed BP recovery, OHypo, and OHyper. Through a latent class mixed model, we tested for significant differences among these four categories, further validating the feasibility of current standards and this classification approach. Our results show that orthostatic BP regulation patterns vary significantly among individuals, with distinct differences in SBP trajectories observed between the four groups. This differentiation underscores the importance of recognizing specific BP recovery profiles in managing and understanding OHypo and its potential impacts on health outcomes.

The association between OHypo and cognitive function is controversial. In the baseline analysis of the Irish Longitudinal Study of Aging (TILDA), participants with OHypo exhibited lower global cognitive performance, especially among women and those with supine hypertension[45,46]. A large and racially diverse sample cross-

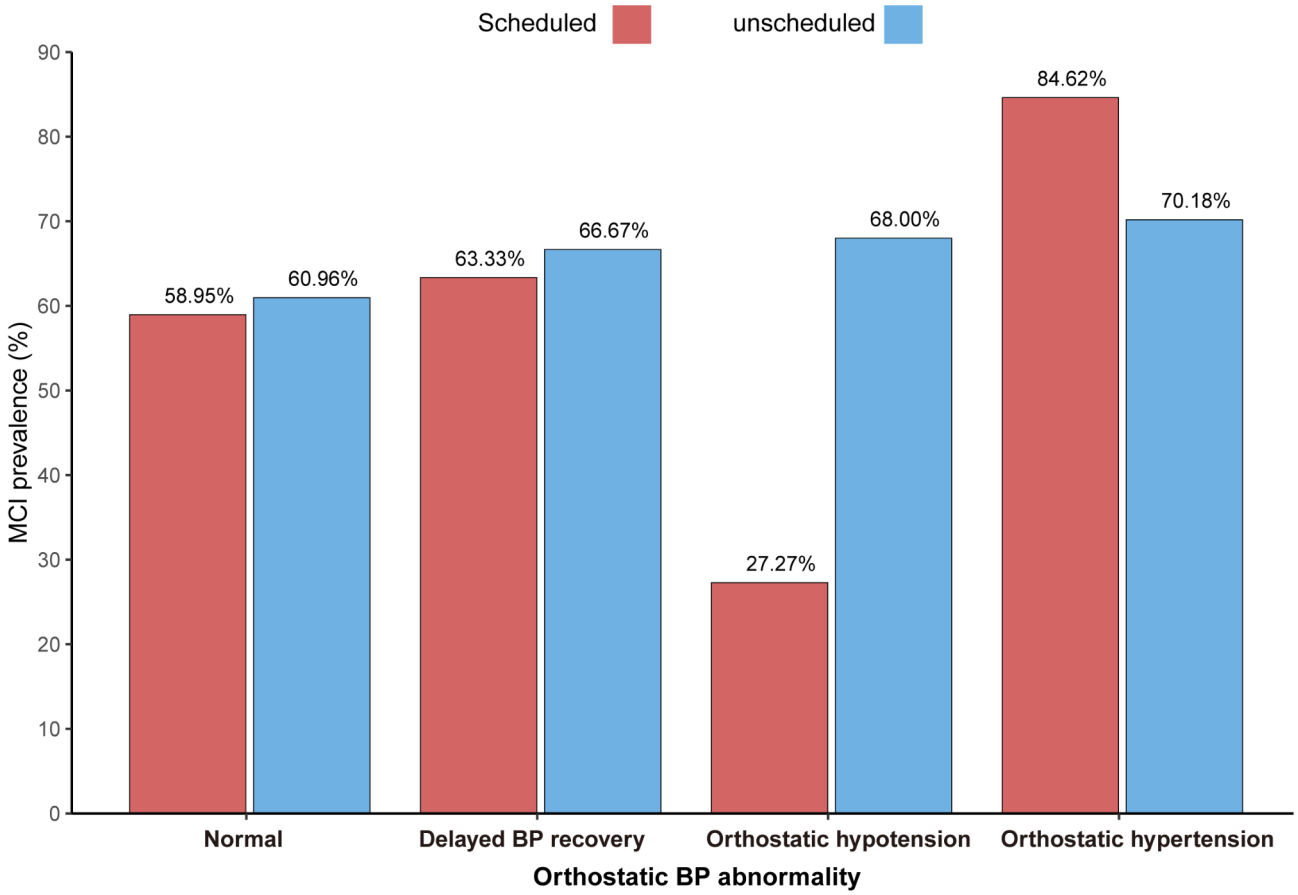

Fig. 2. Prevalence of MCI in each orthostatic BP abnormality groups stratified by regularity of water intake. This figure illustrates the prevalence of mild cognitive impairment in participants with different orthostatic blood pressure abnormalities, stratified by the regularity of water intake. The red bars represent the group with scheduled water intake, while the blue bars represent the group with unscheduled water intake.

sectional study from Brazil investigated the association between OHypo and cognitive performance in 15,105 participants aged 35–74 years old[15]. The study found that both OHypo and OHyper were linked to poorer performance on cognitive function tests among the participants. We found a similar association between OHyper and poor performance in the MoCA-BC scores in our study. A prospective cohort study conducted among elderly individuals(mean age = 68) in Sweden found that not only OHypo but also symptoms of OHypo are risk factors for MCI[47]. However, some studies do not find evidence for the association between OHypo and Cognitive function[17,48–50]. A study involving 184 elderly participants found no statistically significant difference in memory decline between those with OHypo and those without OHypo. In this study, the cognitive function of the 104 OHypo patients was also not associated with recurrent episodes of hypotension[49]. Despite the preliminary findings indicating a correlation between the two at baseline, no association between OHypo and cognitive decline was observed in the follow-up of the TILDA[17]. In addition, a study conducted in China, which included 1347 community-living older adults and assessed cognitive function using the MMSE over a 1 to 2 year follow-up period, also reported no association between OHypo and cognitive decline[50].

On the other hand, opposite results have been reported in other studies. In a prospective cohort study conducted in a rural community in Northern Finland, involving individuals aged 70 and above, the MMSE scores of the OHypo group were slightly higher than those of the non-OHypo group, both at baseline and after a 2.5-year follow-up[51]. A recent study conducted by Saedon et al. in Malaysia found that individuals with OHypo had higher cognitive scores compared to those without OHypo[18]. This finding aligns with our work, where we discovered OHypo to be a protective factor for MCI. Interestingly, Saedon et al.'s study population closely resembles ours; they included individuals aged 55 and above and we include 50 and above, additionally, both were conducted in Asian populations, and both employed the MOCA scale for cognitive assessment. Based on the findings from all studies, it appears that the relationship between OHypo and cognitive function is complex and may vary depending on the population studied, other contextual factors, and the cognitive assessment tools used. One more potential explanation for these inconsistencies in the literature is the variation in water intake patterns across different study populations, which has not been adequately addressed in most prior studies. Hydration status can influence OHypo symptoms and may play a crucial role in modifying the relationship between OHypo and cognitive function. However, many previous studies did not account for this factor, potentially leading to conflicting results. Given that dehydration can exacerbate OHypo symptoms and impact

Variable	OR (95%CI)	*P*
(Intercept)	0.01 (0.00–0.09)	**< 0.001**
Orthostatic BP dysregulation		
Normal recovery	1.000	Ref
Delayed BP recovery	1.03 (0.56–1.93)	0.928
Orthostatic hypotension	0.18 (0.04–0.67)	**0.016**
Orthostatic hypertension	4.09 (1.00–27.77)	0.081
Regularity of water intake, unscheduled	1.07 (0.80–1.42)	0.651
Orthostatic BP abnormality × Regularity of water intake		
Scheduled water intake and normal recovery	1.000	Ref
Unscheduled water intake and delayed BP recovery	1.22 (0.59–2.49)	0.592
Unscheduled water intake and orthostatic hypotension	5.82 (1.17–35.34)	**0.039**
Unscheduled water intake and orthostatic hypertension	0.26 (0.03–1.21)	0.116
Water intake		
< 1000 ml/day	1.000	Ref
1000–2000 ml/day	0.90 (0.67–1.21)	0.482
≥ 2000 ml/day	0.79 (0.56–1.10)	0.161
Age, yrs	1.09 (1.07–1.11)	**< 0.001**
Sex, female	0.82 (0.60–1.12)	0.220
BMI	0.98 (0.95–1.02)	0.333
eGFR	1.01 (0.99–1.02)	0.378
Education		
≤ Primary school	1.000	Ref
Middle school	1.24 (0.95–1.61)	0.112
≥ High School	0.67 (0.48–0.93)	**0.017**
Ethnicity		
Han	1.000	Ref
Mongolian	0.67 (0.53–0.86)	**0.001**
Others	0.48 (0.25–0.92)	**0.027**
Smoking status		
Non-smoking	1.000	Ref
Former smoking	1.76 (1.29–2.42)	**< 0.001**
Current smoking	1.45 (0.88–2.43)	0.145
Alcohol drinking		
Non-drinking	1.000	Ref
Former drinking	0.86 (0.60–1.24)	0.424
Current drinking	0.64 (0.36–1.17)	0.141
Physical labor level		
Low	1.000	Ref
Moderate	0.92 (0.70–1.21)	0.561
High	0.79 (0.56–1.11)	0.169
Diuretics	1.09 (0.41–3.10)	0.868
β-blocker	1.12 (0.36–4.01)	0.846
α-blocker	0.69 (0.20–2.58)	0.568
Vasodilator	1.07 (0.60–1.94)	0.812
SH	0.98 (0.78–1.23)	0.841
Diabetes	1.20 (0.89–1.63)	0.241

Table 2. Moderating effect between scheduled water intake and orthostatic BP dysregulation on MCI using logistic regression model. BP, blood pressure; BMI, body mass index; MCI, mild cognitive impairment; SH, supine hypertension; eGFR, estimated glomerular filtration rate. Significant values are in bold.

cerebral perfusion, differences in hydration habits among study populations could contribute to the observed discrepancies[29]. Additionally, as discussed earlier, the protocol for diagnosing OHypo is rigorous and difficult to implement in clinical practice. Many studies, for convenience, have used a single measurement in standing position, although it was acceptable by the medical community[52]. Differences in assessment criteria, coupled with variations in hydration status, may explain the heterogeneous results reported in the literature. Further research is warranted to indicate the underlying mechanisms and potential modifiers of this relationship.

Variable	β (95%CI)	P
(Intercept)	31.64 (26.63–36.66)	**< 0.001**
Orthostatic BP abnormality		
Normal recovery	1.000	Ref
Delayed BP recovery	0.90 (− 0.48 to 2.28)	0.199
Orthostatic hypotension	2.02 (− 0.83 to 4.88)	0.165
Orthostatic hypertension	− 2.28 (− 4.87 to 0.32)	0.085
Regularity of water intake, unscheduled	− 0.03 (− 0.65 to 0.58)	0.913
Orthostatic BP abnormality × Regularity of water intake		
Scheduled water intake and normal recovery	1.000	Ref
Unscheduled water intake and delayed BP recovery	− 1.56 (− 3.12 to 0.004)	**0.050**
Unscheduled water intake and orthostatic hypotension	− 2.90 (− 6.31 to 0.51)	0.096
Unscheduled water intake and orthostatic hypertension	2.25 (− 0.61 to 5.11)	0.123
Water intake		
< 1000 ml/day	1.000	Ref
1000–2000 ml/day	0.59 (0.02–1.16)	**0.044**
≥ 2000 ml/day	1.34 (0.62–2.06)	**< 0.001**
Age, yrs	− 0.21 (− 0.25 to − 0.17)	**< 0.001**
Sex, female	0.17 (− 0.49 to 0.83)	0.608
BMI	0.00 (− 0.07 to 0.07)	0.988
eGFR	− 0.02 (− 0.04 to 0.005)	0.116
Education		
≤ Primary school	1.000	Ref
Middle school	2.29 (1.76–2.83)	**< 0.001**
≥ High School	3.77 (3.06–4.48)	**< 0.001**
Ethnicity		
Han	1.000	Ref
Mongolian	0.66 (0.15–1.17)	**0.011**
Others	1.68 (0.37–2.99)	**0.012**
Smoking status		
Non-smoking	1.000	Ref
Former smoking	− 1.05 (− 1.69 to − 0.40)	**0.002**
Current smoking	− 0.38 (− 1.39 to 0.63)	0.462
Alcohol drinking		
Non-drinking	1.000	Ref
Former drinking	0.10 (− 0.67 to 0.87)	0.793
Current drinking	0.62 (− 0.59 to 1.83)	0.315
Physical labor level		
Low	1.000	Ref
Moderate	0.09 (− 0.46 to 0.64)	0.744
High	0.51 (− 0.13 to 1.14)	0.118
Diuretics	− 0.45 (− 2.39 to 1.48)	0.645
β-blocker	− 0.14 (− 2.43 to 2.14)	0.901
α-blocker	0.01 (− 2.58 to 2.61)	0.993
Vasodilator	0.52 (− 0.66 to 1.70)	0.384
SH	0.00 (− 0.48 to 0.48)	0.989
Diabetes	− 0.68 (− 1.32 to − 0.04)	**0.037**

Table 3. Moderating effect between regularity of water intake and orthostatic BP abnormality on cognitive scores using liner regression model. BP, blood pressure; BMI, body mass index; MCI, mild cognitive impairment; SH, supine hypertension; eGFR, estimated glomerular filtration rate. Significant values are in bold.

Our study primarily focused on examining the moderating effect of scheduled water intake on the association between OHypo and MCI. Based on our findings, the interaction term between the regularity of water intake and OHypo was statistically significant in the model. Consequently, we performed a subgroup analysis based on whether participants were with or without scheduled water intake. We discovered that the association between OHypo and MCI, as well as MoCA-BC scores, differed between the two groups. This indicates that scheduled

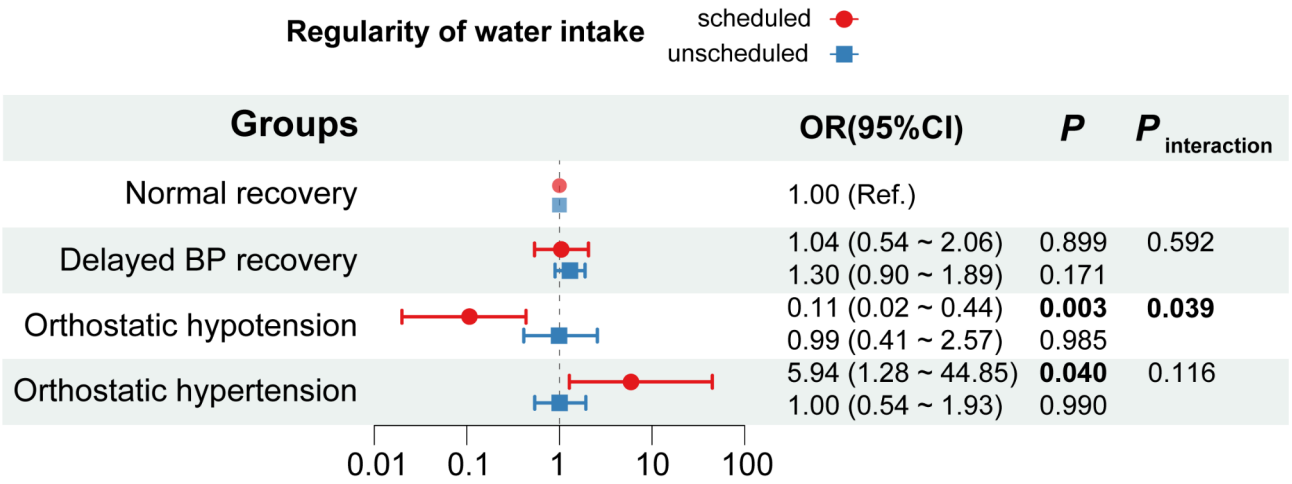

Fig. 3. Association between orthostatic BP dysregulation and MCI modified by regularity of water intake using logistic regression models. Models adjusted for daily water intake, age, sex, BMI, eGFR, education level, ethnicity, smoking, alcohol consumption, physical labor level, medication use (diuretics, α-adrenergic blockers, vasodilators), supine hypertension and diabetes. BP, blood pressure; BMI body mass index; MCI mild cognitive impairment; eGFR estimated glomerular filtration rate

water intake has a moderating effect on the relationship between OHypo and MCI. Specifically, individuals with scheduled water intake exhibited a significantly lower OR for MCI compared to those with unscheduled water intake. This supports the hypothesis that scheduled water intake may play a protective role against cognitive decline in the context of OHypo. Notably, our study utilized MoCA-BC which is considered more sensitive than the MMSE, particularly for detecting impairments in executive function[38]. Given that executive dysfunction is closely linked to vascular changes, this could partly explain our ability to identify associations between OHypo and cognitive performance and the moderating of water intake in the current study. Despite numerous studies confirming the positive role of water intake in managing OHypo patients[28–30], no research has specifically focused on the improvement of cognitive function in OHypo patients through water intake. Furthermore, there is a lack of studies exploring the specific water intake patterns that should be conducted. Our research fills this gap by demonstrating the impact of scheduled water intake on cognitive outcomes in OHypo patients. Notably, our study included rural Chinese adults aged 50 and above, a population that may differ from those in urban or high-income settings. Given the high prevalence of both OHypo and cognitive decline in older populations worldwide, similar populations in other rural areas and in developing countries, which often experience unique challenges related to healthcare access and lifestyle factors that may influence both OHypo and cognitive health, may also benefit from this intervention. Thus future studies should seek to replicate our findings in more diverse populations, including urban and different geographic.

The impact of scheduled water intake probably resulted from the following reasons. OHypo is often perceived as an indicator of inadequate blood volume and compromised peripheral vascular constriction[32]. OHypo has been shown to impair brain perfusion, which play a significant role in the relationship between OHypo and cognitive impairments[47]. Those with intact cerebral autoregulation can maintain stable cerebral blood flow regardless of the sudden BP drop, but those with cerebral autoregulation dysfunction may be at risk of cerebral hypoperfusion hypoxia, brain ischemia, and thus dementia, particularly older adults[53,54]. Dehydration and OHypo can lead to reduced cerebral blood flow, which is thought to contribute significantly to cognitive impairments. The activation of sympathetic adrenergic pathways by water intake leads to peripheral vasoconstriction and increased cardiac output, which help to restore blood pressure and improve circulatory efficiency[28]. This enhanced blood circulation improves cerebral perfusion, ensuring that the brain receives an adequate supply of oxygen and nutrients required for optimal cognitive function. Impaired brain blood flow regulation resulting from OHypo could potentially lead to structural alterations in brain regions, such as white matter rarefaction and gray matter atrophy, which are the foundation of neurodegenerative processes[55]. Conversely, water intake is known to augment blood flow and enhance hemodynamic function, highlighting its potential benefits in mitigating the effects of OHypo on vascular and cognitive health. Additionally, compared to unscheduled water intake, scheduled water intake can assist patients with OHypo in maintaining stable blood volume and BP. By consuming water at regular intervals, fluctuations in blood volume can be minimized, thereby alleviating symptoms arising from sudden drops in BP, such as dizziness and fainting[56]. This regular hydration pattern helps to stabilize blood pressure and prevent cognitive disruptions associated with acute blood pressure changes. Furthermore, in addition to these vascular effects, proper hydration also plays a vital role in neural conductivity as it helps maintain the electrolyte balance, ensuring efficient synaptic signaling and supporting cognitive processes[57]. Future research should focus on longitudinal studies that examine the association between scheduled water intake and cognitive outcomes for individuals with OHypo. Additionally, experimental studies using animal models could further investigate the physiological mechanisms underlying these associations

in a controlled environment. These studies could provide new insights into the potential role of hydration in managing OHypo and preventing cognitive decline.

Our study has several key strengths. This is the first study to investigate the regularity of water intake on cognition in patients with OHypo. Notable strengths include the large sample size, the use of a well-validated cognitive assessment tool, MoCA-BC, and comprehensive data on participants' water intake patterns and orthostatic BP measurements. However, some limitations require caution in interpreting and generalizing our findings. Firstly, it is important to acknowledge that our study was conducted within a community-based cohort and we used a more rigorous criteria of OHypo, and as a result, the sample size of participants with OHypo was relatively small. Future studies could be conducted from targeting specialized patient cohorts, such as those with clinically diagnosed OHypo, or expanding the sample size within community settings to ensure sufficient representation of individuals with OHypo. The cross-sectional design limits the ability to establish causality between water intake patterns, orthostatic BP abnormalities, and cognitive function. To establish causality, future research should employ longitudinal designs that allow for the causality and directionality of the observed associations. Additionally, the study relied on self-reported water intake, which may be subject to recall bias and inaccuracies. Participants may have over- or under-reported their actual water intake, which could have influenced the results. Objective measures, such as hydration biomarkers, such as calculated serum osmolarity[58], or more precise tracking of water intake, would help to overcome this limitation. Lastly, some confounders, such as cardiovascular risk factors, other conditions that cause orthostatic intolerance, particularly vasovagal syncope and postural tachycardia syndrome, may not have been fully adjusted in this study and future research should account for these confounders in their analyses to provide a clearer understanding of the relationships.

Conclusion

In conclusion, our study provides evidence that scheduled water intake moderate the association between OHypo and MCI, highlighting the potential of scheduled water intake, as a simple, cost-effective intervention for managing cognitive decline in OHypo patients. The complex relationship between OHypo, MCI, and hydration status necessitates continued research to uncover underlying mechanisms and develop targeted strategies for improving cognitive outcomes in OHypo patients. By addressing these gaps in knowledge and considering the potential benefits of scheduled water intake, healthcare providers can use non-drug management to better support the cognitive health and overall well-being of individuals with OHypo.

Data availability

The relevant anonymized participants' data, full dataset, technical appendix, and statistical code are available on reasonable request from the corresponding author.

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Author contributions

YW, WF and QC conceived and designed the study. MH, HB, RP and BL collected the data. YW and WF prepared the manuscript and analyzed the data; all authors reviewed the manuscript; MM, NT and LZ substantively revised the manuscript; LZ, NT and MM had the primary responsibility for the final content. All authors have contributed to drafting the manuscript and approving the final version. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
The studies involving human participants were reviewed and approved by the procedures followed were performed under the ethical standards of the responsible committee on human experimentation of China Medical University ([2018]083).

Consent to participate
All the participants provided their written informed consent to participate in this study.

Additional information
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