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Gender differences in the association between physical activity and cognitive subdomains among elders with type 2 diabetes and mild cognitive impairment: a cross-sectional study

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ABSTRACT

Objectives The objective of this study was to evaluate the gender differences in the correlation between physical activity (PA) and cognitive subdomains in elderly individuals with type 2 diabetes (T2D) and mild cognitive impairment (MCI).

Design Cross-sectional study.

Setting The research was carried out in communities located in Fuzhou, Fujian Province and Beijing Municipality.

Participants Community-dwelling elders with T2D and MCI aged 60 years or older were eligible for this study.

Primary outcome measures and analyses The weekly PA score was assessed using the International Physical Activity Questionnaire (IPAQ). The cognitive subdomains were evaluated through a battery of cognitive assessments, including the Rey Auditory Verbal Learning Test (RAVLT), Trail Making Test Part B, Digit Symbol Substitution Test (DSST) and the Stroop Color-Word Test (SCWT). Multiple linear regression models were employed to examine the association between PA and cognitive subdomains in both male and female individuals.

Results In older men, higher total IPAQ score was positively correlated with higher RAVLT (P=0.011) and SCWT (P=0.049). There was a significant interaction between the total PA score and gender in relation to RAVLT (P=0.008) and SCWT (P=0.027). Moreover, there was a positive correlation between moderate-vigorous PA level and RAVLT in older men (P=0.007). Additionally, a positive correlation was found between moderate-vigorous PA level and DSST in older women (P=0.038).

Conclusion In older individuals with T2D and MCI, the association between PA and cognitive subdomains differs between men and women. This discrepancy may impact the customisation of exercise recommendations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study was conducted at the community level, and the findings can be extrapolated to the broader population.
⇒ The study examined different subgroups of physical activity (PA) at moderate-vigorous and walking intensities, and cognitive subdomains encompassed various dimensions such as memory, attention, executive function and processing speed.
⇒ The utilisation of the International Physical Activity Questionnaire may introduce recall bias, prompting the suggestion that accelerometers could be employed in future studies to provide an objective assessment of PA.
⇒ It was a cross-sectional study and therefore a causal relationship between PA and cognitive subdomains cannot be inferred.

BACKGROUND

The incidence of diabetes is on the rise in both developing and developed nations, attributed to changes in socioeconomic conditions and an increase in unhealthy lifestyle habits. According to the International Diabetes Federation, the number of patients in China of having diabetes was about 1.409 million,[1] which represented a significant increase compared with the results of the same survey conducted in 2019 (1.289 million). Nearly 95% of diabetic cases are type 2 diabetes (T2D).[2] Cognitive impairment is a common comorbidity of diabetes, especially in elderly populations.[3] Our previous meta-analysis found that about 45% of people with diabetes have mild cognitive impairment (MCI).[4] MCI is a transitional condition between normal cognitive function and dementia.[5] Moreover, diabetics are 1.5–3 times more likely to progress from MCI to dementia compared with non-diabetics.[6] Patients with T2D and MCI experience cognitive impairments in memory, executive function, attention and processing speed.[7–9] Impaired cognitive function may lead to compromised self-management in patients with T2D, exacerbating their condition and heightening the risk of complication.

Physical activity (PA) is a promising non-pharmacological behavioural strategy. Regular PA improves blood sugar control in patients with diabetes. A growing body of research has found that PA also enhances cognition and brain function, and reduces the risk of MCI progressing to dementia.[10–12] Our previous study, which used data from the China Health and Retirement Longitudinal Study, discovered that PA may help prevent some of the potential decline in episodic memory among middle-aged diabetic patients. Similarly, meta-analyses have found that exercise significantly improves global cognitive function in elderly patients with T2D.[13] But the evidence in cognitive subdomains is limited and inconsistent.[14 15] PA levels differ between male and female with T2D.[16] Different genders exhibit distinct physiological responses to exercise, which can impact their cognitive function differently. It is unclear whether there is a correlation between the gender-based variation in PA and its cognitive subdomains. Thus, the aim of this study was to assess the gender differences in the association between PA and cognitive subdomains among elderly individuals with T2D and MCI.

METHODS

Study subjects and sample size

This cross-sectional community-based study was conducted between May and December 2020. Subjects were recruited from communities located in Fuzhou, Fujian Province and Beijing Municipality. Upon receipt of a roster of patients diagnosed with T2D from the community, each patient has been contacted, extended an invitation to partake and a personalised appointment has been arranged. Patients who expressed interest in participating were presented with a detailed description of the study and were given the choice to volunteer or decline participation. When they agreed to participate in the study, the clinical research coordinator evaluated their eligibility based on predefined inclusion and exclusion criteria. The inclusion criteria encompassed (1) a clinical diagnosis of T2D,[17 18] (2) presence of MCI without dementia,[19] (3) age 60 years or older, and (4) informed consent and voluntary participation. Exclusion criteria included (1) cognitive impairment caused by other causes such as drug use and poisoning, (2) subjects unable to comply with the assessment due to severe aphasia, visual or hearing impairments, or illiteracy, and (3) individuals involved in other studies that may impact the current research. A total of 299 elderly patients aged 60 years and above with T2D and MCI were recruited for the study. These participants provided PA data and underwent subcognitive assessments. The magnitude of the Spearman correlation coefficient between PA scores and global cognitive level was 0.102.[20] The two-sided CI width was 0.2, and the confidence level was $1-\alpha=0.90$. A sample size of N=267 cases was determined using PASS V.15 software.

Sociodemographic information

Sociodemographic data were gathered in accordance with the literature on risk factors associated with cognitive impairment and were evaluated by experts before the commencement of the study. Age, years of education, duration of diabetes, blood pressure, smoking status, alcohol consumption, use of diabetes medications and history of disease were collected through self-reported measures. Measurements of height, weight, waist circumference and hip circumference were conducted on-site. Subjects were instructed to wear light clothing and refrain from wearing shoes during weight measurements, which were recorded to the nearest 0.1 kg. Height measurements were recorded to the nearest 0.5 cm. Body mass index (BMI) was computed by dividing weight (in kilograms) by the square of height (in metres). Waist circumference was assessed at the midpoint between the lowest rib and the upper edge of the iliac crest, while hip circumference was measured at the level of the greater trochanter. The waist-to-hip ratio (WHR) was calculated as the waist circumference divided by the hip circumference.

Laboratory serum biochemical tests

Subjects were instructed to fast overnight, and venous blood samples were collected in the morning on an empty stomach. Serum levels of fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TGs), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were assessed using an ABBOTT ARCHITECT C16000 automated biochemistry analyser (ABBOTT, USA). Additionally, serum levels of glycated haemoglobin (HbA1c) were determined using a Bio-Rad D-100 HbA1c analyser (Bio-Rad, USA).

Assessment of PA

PA level was evaluated using the long form of International Physical Activity Questionnaire (IPAQ-L).[21] In brief, IPAQ-L consisted of 27 questions, 25 focusing on the respondent's PA levels and 2 addressing sedentary behaviour. Participants were queried regarding their PA over the preceding 7 days. Within each category of PA, participants were also queried about the frequency over a 1-week period and the total daily duration of PA at various intensities, such as vigorous-intensity activities, moderate-intensity activities and walking. Only activities with a duration of at least 10 min were taken into account in the questionnaire. Metabolic equivalent (min/week) in the PA domain is determined through the IPAQ scoring system.

Subcognitive assessment

The Rey Auditory Verbal Learning Test (RAVLT) was administered to assess memory.[22] The total score of the five immediate recalls of the 15-word list was used for statistical analysis. The attention level was assessed through the Digit Symbol Substitution Test (DSST),[23] which measures the quantity of accurate substitutions completed within a 90-second time frame. The Trail

Table 1 Demographic and clinical biochemical data of subjects by gender

Varies	Male (N=140)	Female (N=159)	*P* value
Age (years)	68.97±5.21	69.11±5.56	0.824
Height (m)*	1.62±6.85	1.62±7.41	0.666
Weight (kg)*	63.68±11.39	62.67±10.04	0.798
Body mass index (m/kg^2)*	24.17±3.80	23.89±3.12	0.448
Waist-to-hip ratio*	0.92±0.05	0.91±0.1	<0.001
Duration of diabetes (year)*	10.66±6.92	9.61±6.14	0.271
Years of education*	10.18±3.74	8.96±3.70	0.005
Comorbid illness, no			0.823
≤1	102 (72.9)	114 (71.7)	
>1	38 (27.1)	45 (28.3)	
Smoking			<0.001
Never	55 (39.3)	158 (98.1)	
Former	51 (36.4)	2 (1.3)	
Current	34 (24.3)	1 (0.6)	
Alcohol consumption			<0.001
Never	76 (54.3)	147 (92.5)	
Former	25 (17.9)	9 (5.7)	
Current	39 (27.9)	3 (1.9)	
Blood pressure, mm Hg			
Systolic	130 (18)	129 (15)	0.472
Diastolic	80 (15)	78 (10)	0.068
Blood biochemistry data			
Fasting blood glucose (mmol/L)*	7.51±1.84	7.73±1.90	0.205
Glycated haemoglobin (%)*	6.79±1.31	6.88±1.12	0.170
Total cholesterol (mmol/L)*	4.54±0.93	4.83±0.91	0.071
Triglycerides (mmol/L)*	1.66±1.36	1.76±0.73	0.001
High-density lipoprotein (mmol/L)*	1.47±0.77	1.50±0.73	0.082
Low-density lipoprotein (mmol/L)*	2.39±0.79	2.49±0.75	0.544
Diabetes medications, n (%)			
Metformin	88 (62.9)	90 (56.6)	0.272
Sulfonylurea	35(25)	38 (23.9)	0.825
Thiazolidinediones	2 (1.4)	5 (3.1)	0.454
α-glucosidase inhibitor	43 (30.7)	40 (25.2)	0.284
DPP-4 inhibitor	3 (2.1)	4 (2.5)	1.0
SGLT2 inhibitor	1 (0.7)	0 (0)	0.468
Insulin	9 (6.4)	11 (6.9)	0.866

*Data did not meet the assumption of normality.
DPP-4, dipeptidyl peptidase 4; SGLT2, sodium-glucose co-transporter-2.

Making Test Part B (TMT-B) is an assessment of executive function that measures the time taken (in seconds) to complete the task.[24] Assessment of processing speed was through the administration of the Stroop Color-Word Test (SCWT).[25] Higher scores were deemed indicative of better performance on the tests, except for the SCWT and TMT-B tasks, where longer completion times were associated with poorer performance. All assessments were conducted by trained professionals.

Statistical analysis

Continuous data are described using the mean±SD. Comparison of continuous variables with a normal distribution between two groups was conducted using

Table 2 Comparison of physical activity (PA) by different intensities of activity between genders

Varies	Male (N=140)	Female (N=159)	*P* value
Vigorous (MET min/week)*	234±922.37	77.99±407.42	0.095
Moderate (MET min/week)*	1693.89±1603.85	2976.92±1825.48	<0.001
Walking (MET min/week) *	1675.16±1259.83	1278.08±1043.03	0.006
Sedentary time (min/day) *	67.88±33.87	60.51±35.12	0.055
PA total (MET min/week) *	3603.06±1986.18	4332.99±2159.71	0.002

*Data did not meet the assumption of normality.
MET, metabolic equivalent.

independent t-tests, while non-normally distributed variables were compared using Wilcoxon tests. Categorical variables are typically presented using numbers and percentages, and used the χ^2 test or Fisher's exact test. Multiple linear regression models were employed to examine the association between PA and cognitive subdomains in both male and female participants, interaction between PA and gender, adjusted for age, years of education, duration of diabetes, FBG, TC, WHR, BMI, smoking status and alcohol consumption. In order to mitigate the influence of the original unit of measurement, all parameters were Z-score transformed in the multiple linear regression model. All statistical analyses were conducted using the IBM SPSS V.24 software program.

Patient and public involvement

No patients or members of the public were involved in the design, conduct or reporting of this research.

RESULTS

A total of 299 patients diagnosed with T2D and MCI were part of this analysis, with 149 of them being male (46.8%). Table 1 presents the clinical characteristics of the study participants categorised by gender. There were no significant differences observed in BMI, duration of diabetes, FBG, HbA1c, TC, HDL, LDL, prevalence of hypertension and coronary disease, as well as the utilisation of diabetes medications and insulin between male and female participants. The male subjects exhibited significantly higher WHR values (p<0.001) and years of education (p=0.005), whereas female participants showed higher TG levels (p=0.001).

Table 3 Comparison of cognitive subdomains between genders

Varies	Male (N=140)	Female (N=159)	*P* value
Memory			
RAVLT (number)	29.73±9.60	33.09±10.43	0.011
Attention			
DSST (score)	29.89±9.21	29.09±9.6	0.448
Executive function			
TMT-B (s)*	220.11±90.26	238.28±98.84	0.058
Processing speed			
SCWT colour (s)*	22.17±7.12	21.13±7.41	0.109
SCWT colour (number)*	0.597±1.41	0.46±1.13	0.463

*Data did not meet the assumption of normality.
DSST, Digit Symbol Substitution Test; RAVLT, Rey Auditory Verbal Learning Test; SCWT, Stroop Color-Word Test; TMT-B, Trail Making Test Part B.

Tables 2 and 3 present the differences in different activity intensities and cognitive subdomains between genders, respectively. The total IPAQ score was found to be significantly higher in female compared with male participants (4332.99±2159.71 vs 3603.06±1986.18, p=0.002). The older women exerted more moderate-intensity activity level (2976.92±1825.48 vs 1693.89±1603.85, p<0.001), whereas older men had a higher level of walking-intensity activity (1675.16±1259.83 vs 1278.08±1043.03, p=0.006). Energy expenditure during vigorous-intensity activity and sedentary time did not differ between genders. Furthermore, older women outperformed men in the RAVLT (p=0.011). However, there were no differences between male and female participants in other cognitive subdomains.

Multiple linear regression analysis showed that higher PA levels in male participants were positively associated with RAVLT and time of SCWT (β=0.214, p=0.011; β=−0.171, p=0.049) after adjusting for age, years of education, duration of T2D, FBG, TC, WHR, BMI, smoking status and alcohol consumption. No such association was observed in female participants (table 4). However, there was a significant interaction between the total IPAQ score and gender on RAVLT and the time of SCWT (β=0.164, p=0.008; β=−0.139, p=0.027).

Taking further consideration of activity intensity, multiple linear regression analysis (table 5) showed that higher level of moderate-vigorous PA level in male participants was positively associated with RAVLT (β=0.227, p=0.007), while a higher level of moderate-vigorous PA level in female participants was positively associated with DSST (β=0.153, p=0.038).

Table 4 The association between total physical activity (PA) score and cognitive subdomains

Varies	Male (N=140)		Female (N=159)		Gender×total PA	
	Std β	Std 95% CI	Std β	Std 95% CI	Std β	Std 95% CI
RAVLT (number)	0.214*	0.050, 0.378	0.077	−0.083, 0.236	0.164*	0.043, 0.285
DSST (score)	0.156	−0.008, 0.331	0.087	−0.060, 0.234	0.066	−0.051, 0.182
TMT-B (s)	−0.081	−0.255, 0.091	−0.047	−0.188, 0.094	−0.012	−0.132, 0.108
SCWT colour (s)	−0.171*	−0.355, 0.001	−0.065	−0.219, 0.090	−0.139*	−0.261, 0.016
SCWT colour (number)	−0.008	−0.216, 0.197	0.099	−0.053, 0.226	0.01	−0.123, 0.126

Adjusted for age, years of education, duration of diabetes, fasting blood glucose, waist-to-hip ratio, body mass index, smoking status, alcohol consumption and total cholesterol.
*P<0.05; **P<0.01.
DSST, Digit Symbol Substitution Test; RAVLT, Rey Auditory Verbal Learning Test; SCWT, Stroop Color-Word Test; TMT-B, Trail Making Test Part B.

DISCUSSION

As far as we know, this is the first study to explore the differences in relationship between PA and cognitive subdomains among older patients with T2D and MCI, separated by gender. Results of the study illustrate a significant interaction between the total IPAQ level and gender on memory and processing speed. Further sensitivity analysis revealed that there was an effect of moderate-vigorous PA on memory in older men and attention in older women.

Previous research has found that male patients with T2D have higher levels of PA than female patients.[26] In our sample, we found that older women engaged in higher total PA and moderate-intensity PA compared with older men. It is well-known that men and women play different social roles. In our study, the participants were retired elders. Women were more likely than men to engage in domestic activities that were moderately physically exhausting. A previous study in a cognitively normal sample of elderly individuals with T2D found that women performed better than men on verbal memory tasks.[27 28] Gender differences in cognitive domains persist even in the presence of the disease. In the sample with amnestic MCI, women showed better verbal memory than men.[29] We found similar results in patients with T2D and MCI. However, unlike previous studies, our findings did not identify differences in attention, executive function and processing speed among older patients with T2D and MCI based on gender. In elders with T2D and MCI, memory function is generally better in female than in male participants, and the possible mechanism for this remains unclear. Sex hormones are neuroprotective in both sexes,[30] and oestrogen may play an important role in cognitive differences. Oestrogen receptors are abundant in the human hippocampus and prefrontal cortex, which are involved in memory.[31] Previous animal research indicates that oestradiol is the most important oestrogen for preserving hippocampal function, and memory is affected by the relative expression of oestrogen receptors as they interact with oestradiol.[32] The results of a longitudinal study suggest that verbal memory declines in women during perimenopause but returns to premenopausal levels after menopause.[33] Our study sample consisted of individuals older than 60 years, with the majority of female

Table 5 Results of the sensitivity analysis: the association between physical activity and cognitive subdomains, according to different genders and intensities of activity

Varies	Male (N=140)				Female (N=159)			
	Moderate-vigorous		Walking		Moderate-vigorous		Walking	
	Std β	Std 95% CI	Std β	Std 95% CI	Std β	Std 95% CI	Std β	Std 95% CI
RAVLT (number)	0.227**	0.064, 0.393	0.018	−0.129, 0.161	0.045	−0.118, 0.214	0.073	−0.094, 0.261
DSST (score)	0.105	−0.063, 0.281	0.097	−0.060, 0.235	0.153*	0.009, 0.311	−0.092	−0.268, 0.059
TMT-B (s)	−0.078	−0.253, 0.095	−0.018	−0.166, 0.134	−0.085	−0.237, 0.055	0.055	−0.093, 0.221
SCWT colour (s)	−0.148	−0.333, 0.025	−0.061	−0.210, 0.100	−0.140	−0.306, 0.013	0.114	−0.042, 0.301
SCWT colour (number)	0.019	−0.186, 0.230	−0.038	−0.217, 0.139	0.026	−0.122, 0.170	0.150	−0.005, 0.304

Adjusted for age, years of education, duration of diabetes, fasting blood glucose, waist-to-hip ratio, body mass index, smoking status, alcohol consumption and total cholesterol.
*P<0.05; **P<0.01.
DSST, Digit Symbol Substitution Test; RAVLT, Rey Auditory Verbal Learning Test; SCWT, Stroop Color-Word Test; TMT-B, Trail Making Test Part B.

participants in a postmenopausal state. Even if oestrogen levels fall with age, women may offset the neurodegenerative damage linked to T2D by maintaining oestrogen receptor signalling in the brain.[34] However, it is not clear whether or how sex hormone changes are associated with cognitive subdomains, specifically processing speed.

Women and men exhibit distinct physiological responses to exercise. Specific forms of exercise at the same intensity and dose may have different impacts on male versus female due to their distinct physiological responses.[35] PA may promote brain and cognitive health differently in male and female. We observed differential patterns between male and female regarding the associations of cognitive variables with PA. Total PA retained a statistically significant association with memory function in male. Previous studies have found that a significant inverse association between PA and amyloid burden was found only in men.[36] In addition, higher cardiopulmonary fitness levels were associated with smaller ventricular volume and larger volumes of the temporal and parietal lobes, particularly the precuneus, in men but not in women. Interestingly, however, we found that moderate-vigorous PA has an effect on memory in older men and attention in older women. Although the exact mechanism is unclear, these results may provide a basis for further exercise intervention studies targeting cognitive impairments, specifically memory in men or attention in women. Indeed, our findings extend previous observations and suggest that the relationship between cognitive variables and PA depends on gender-related factors, although the underlying mechanisms have not been completely understood yet. Further studies are needed to better understand the factors driving these gender-dependent mechanisms. Developing personalised, tailored exercise recommendations to promote healthy brain ageing should take gender differences into account.[37]

This study has several limitations. First, because this was a cross-sectional study, no causal relationships could be established. A prospective cohort study will be conducted using this study as reference. Second, our PA scale uses the IPAQ, known for its good reliability and validity. But it is not as accurate as an objective measure of PA. Finally, although our inclusion criterion was age ≥60 years, our data show that the age range of the sample is 60–75 years. Extrapolation is limited by the lack of data for adults older than 75 years.

CONCLUSION

In conclusion, this study found that the association between PA and cognitive subdomains varied by gender in elders with T2D and MCI. Higher total PA in men was associated with better memory function. There was an effect of moderate-vigorous PA on memory in older men and attention in older women. This may influence gender-specific personalised interventions for elderly individuals with T2D and MCI.

Contributors JT, JH, YX and ZL contributed to study design, data collection and analysis that were performed by YC, PZ, YY and SG. The first draft of the manuscript was written by JX. ZL: the guarantor for the overall content. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by the Ethics Committee of the Second People's Hospital Affiliated to Fujian University of Traditional Chinese Medicine (approval no. 2020KY-004-02) and Xiyuan Hospital of China Academy of Chinese Medical Sciences (approval no. 2020XLA033-2). Prior to participation, each subject provided written informed consent.

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Data availability statement All data relevant to the study are included in the article.

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