Heliyon 10 (2024) e35292

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Quantitative gait markers and the TUG time in chronic kidney disease

Xin Zhang [a,b,1], Hao Wang [a,b,1], Heyang Lu [c], Min Fan [d], Weizhong Tian [e], Yingzhe Wang [b,f], Mei Cui [b,c], Yanfeng Jiang [b,f], Chen Suo [a,b], Tiejun Zhang [a,b], Li Jin [b,f], Kelin Xu [a,b,*], Xingdong Chen [b,f,g,h,**]

[a] School of Public Health, The Key Laboratory of Public Health Safety of Ministry of Education, Fudan University, Shanghai, China
[b] Fudan University Taizhou Institute of Health Sciences, Taizhou, Jiangsu, China
[c] Department of Neurology, Huashan Hospital, Fudan University, Shanghai, China
[d] Taixing Disease Control and Prevention Center, Taizhou, Jiangsu, China
[e] Taizhou People's Hospital Affiliated to Nantong University, Taizhou, Jiangsu, China
[f] State Key Laboratory of Genetic Engineering, Zhangjiang Fudan International Innovation Center, School of Life Sciences, Human Phenome Institute, Fudan University, Shanghai, China
[g] National Clinical Research Center for Aging and Medicine, Huashan Hospital, Fudan University, Shanghai, China
[h] Yiwu Research Institute of Fudan University, Yiwu, Zhejiang, China

ARTICLE INFO

Keywords:
Chronic kidney disease
Fall
Gait
Mediation analysis

ABSTRACT

Background: Poor gait performance results in more fall incidents among people with chronic kidney disease (CKD). It is unknown what specific quantitative gait markers contribute to high fall risk in CKD and the size of their mediation effects.

Methods: We included 634 participants from the Taizhou Imaging Study who had complete gait and laboratory data. Quantitative gait assessment was conducted with a wearable insole-like device. Factor analysis was utilized to summarize fifteen highly correlated individual parameters into five independent gait domains. Prevalent CKD was defined as an estimated glomerular filtration rate (eGFR) $<$ 60 ml/min per 1.73 m^2, which was calculated based on cystatin C. Regression models were created to examine the associations of prevalent CKD with quantitative gait markers and the TUG time. Mediation analysis was used to investigate whether poor quantitative gait parameters could be mediators and the proportion of their mediation effects.

Results: Participants with prevalent CKD had a higher TUG time (odds ratio = 2.02, $P = 0.025$) and poor gait performance in the phase domain (standardized $\beta = -0.391$, FDR = 0.009), including less time in the swing phase (standardized $\beta = -0.365$, FDR = 0.027) and greater time in the double-support phase (standardized $\beta = 0.367$, FDR = 0.027). These abnormalities mediated the association of prevalent CKD with a high TUG time (for the swing phase: 31.6 %, $P_{mediation} = 0.044$; for the double-support phase: 29.6 %, $P_{mediation} = 0.042$; for the phase domain: 26.9 %, $P_{mediation} = 0.048$).

* Corresponding author. School of Public Health, The Key Laboratory of Public Health Safety of Ministry of Education, Fudan University, Shanghai, China.
** Corresponding author. State Key Laboratory of Genetic Engineering, Zhangjiang Fudan International Innovation Center, School of Life Sciences, Human Phenome Institute, Fudan University, Shanghai, China.
E-mail addresses: xukelin@fudan.edu.cn (K. Xu), xingdongchen@fudan.edu.cn (X. Chen).
[1] Contributed equally.

https://doi.org/10.1016/j.heliyon.2024.e35292
Received 2 May 2024; Received in revised form 23 July 2024; Accepted 25 July 2024
Available online 3 August 2024

Conclusion: Poor phase-related gait abnormalities mediated the relationship between CKD and a high TUG time, suggesting that incorporating quantitative gait markers in specific domains may improve fall prevention programs for individuals with CKD.

1. Introduction

As a highly prevalent condition, chronic kidney disease (CKD) is estimated to affect 9.1 % (mainly stages 1–2) of the world's population, and its burden is becoming substantial with population aging [1]. CKD is defined as a persistent abnormality in kidney structure or function for more than 3 months [2]. It is also a significant risk factor for cardiovascular diseases, correlating with an elevated risk of cardiovascular-related fatalities [1], and has become an important public health problem in China [3]. Older adults, including 55-65 adults, with CKD are prone to falls due to a complex interaction of comorbidities, such as renal osteodystrophy, muscle weakness, and impaired mobility [4]. Therefore, it is urgent to identify the markers of functional decline in the CKD population to prevent the occurrence of falls, which would help to take preventive measures to improve health outcomes.

Based on the coordination among the nervous, skeletal muscle, and cardiovascular systems, abnormal gait performance can reflect decreased physical function and predict fall risk [5,6]. People with CKD have been observed with poor gait performance, especially spatiotemporal parameters [7,8], which is often assessed by cost-effective standardized tests in clinical settings for a specific situation. During the clinical evaluation, the researchers visually observe the walking process of the subjects and then evaluate according to their experience or the items specified in the scales. This method of observation refers to qualitative analysis. However, quantitative gait measurement is superior to clinical examination in the following aspects. First, it could be carried out efficiently in any setting once proper equipment is available. It can also obtain large amounts of objective and accurate spatiotemporal data in a relatively short period without complicated clinical training. Furthermore, these subtle gait data could be categorized into independent domains, each representing unique clinical or even subclinical information [9]. However, few studies have investigated the predictive value of spatiotemporal gait abnormalities to falls in CKD so far. Existing research only revealed the association between kidney dysfunction and gait abnormalities as well as their interactions on falls [10,11]. It is unclear to what extent these subtle gait abnormalities explain a higher TUG time in CKD. Therefore, identifying the quantitative gait markers of high fall risk in the CKD population needs further research.

This population-based study examined the associations of CKD with the TUG time and spatiotemporal gait abnormalities. In addition, we investigated what specific gait parameters or domains and to what extent contribute to high TUG time in CKD to find potential gait signs for fall prevention.

2. Materials and methods

2.1. Design and study population

A cross-sectional study was conducted on a sample of community-dwelling 55-65 adults. Participants were enrolled in the Taizhou Imaging Study (TIS), an ongoing community-based cohort study, the design of which has been described previously [12]. The participants of the TIS are: [1] aged from 55 to 65 [2]; Han Chinese and residing in Taixing for >10 years [3]; free of physician-diagnosed dementia, stroke, cancer, psychiatric disorders, severe liver, or renal disease [4]; able to walk, communicate, participate in physical examinations, and provide informed consent normally and independently [5]; free of MRI contraindications, such as claustrophobia [12]. Among the 904 individuals in baseline, 809 participants had blood samples with complete serum cystatin C data. Exclusion criteria for our study included missing data for gait (n = 160) and a history of fracture (n = 15). The final analysis included 634 participants (Fig. S1). TIS was approved by the Ethics Committee of the School of Life Sciences, Fudan University, Shanghai, China (Institutional Review Board Approval No. 496) and Fudan University Taizhou Institute of Health Sciences (Institutional Review Board Approval No. B017). An informed consent was obtained from all subjects before enrollment.

2.2. Study measures

Kidney function was evaluated using the estimated glomerular filtration rate (eGFR), calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; $eGFR = 141 \times min(Scr/\kappa, 1)^{\alpha} \times max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.108^{if\ female} \times 1.159^{if\ black}$, Scr is serum creatinine κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males [13]. Compared with creatinine-estimated GFR, cystatin C eGFR (eGFRcys) could offer a measure independent of muscle mass [14]. Thus, to avoid the influence of muscle mass on outcomes, we used the CKD-EPI cystatin C equation to calculate eGFRcys: $eGFRcys = 133 \times min(Scys/0.8, 1)^{-0.499} \times max(Scys/0.8, 1)^{-1.328} \times 0.996^{Age} \times 0.932^{if\ female}$, Scys is serum cystatin C (13). Morning fasting blood samples were stored in the cryogenic refrigerator to ensure quality and then transported to the laboratory of Fudan University Taizhou Institute of Health Sciences through the cold chain for subsequent processing. Serum cystatin C was analyzed using an automatic biochemical analyzer (TBA-40FR; TOSHIBA Corp., Tokyo, Japan). CKD is categorized into different stages according to the eGFR. The stages 1–5 are defined as follows: eGFR ≥90; 60 ≤ eGFR <90; 30 ≤ eGFR <59; 15 ≤ eGFR <30; eGFR <15. The higher the stage of CKD, the more severe the kidney dysfunction. CKD staging assists doctors in evaluating the kidney health of patients, devising personalized

treatment plans, and forecasting the progression and prognosis of the disease [2]. Participants in our study with eGFRcys <60 ml/min per 1.73 m^2 were considered to have prevalent CKD (15). Because there were few people in stages 4–5 (stage 4, N = 3; stage 5, N = 0), stratified analysis was carried out based on functional stages defined as follows: 60 ≤ eGFR <90, and 30 ≤ eGFR <59, compared with eGFR ≥90 mL/min/1.73 m^2 [15].

Quantitative gait data in multiple dimensions were obtained using a gait tracking device embedded in insoles (Senno gait, Sennotech Co. Ltd., China). The gait device includes a 16 pressure sensors array and a 9-axis inertial measurement unit. The 16 pressure sensors were tested by the TA. XTplus Texture Analyser, achieving an accuracy rate of over 95 % for the pressure values. When comparing the SennoGait with the SparkFun 9DoF Razor IMU M0, the Pearson correlation coefficients between the two were higher than 0.8 (16). Additionally, participants performed a 14-m flat ground walk wearing shoes equipped with SennoGait to verify the device's capability in gait feature extraction, using a Vicon motion capture system as the reference data. The results showed the accuracy rate above 90 % [16]. With insoles comfortably placed in their shoes, participants walked at their usual pace in a straight line forth and back, including a total of 20 m. The gait parameters for each stride we collected throughout this procedure included stride time, stance time, swing time, stance time percentage of the gait cycle (%GC) symmetry, swing time (%GC) symmetry, stride time symmetry, stride time coefficient of variation (CV), stance time CV, swing time CV, heel strike angle, stride length, maximum swing velocity, gait velocity, swing time (%GC), and double support time (%GC). The definitions of each gait parameter are exhibited in Table S1. Symmetry variables are metrics used to quantify the symmetry of limb movement in gait. It may indicate the presence of muscle strength imbalance, limited joint mobility, or other issues affecting gait if the stance phase or swing phase time on one side is significantly longer than on the other.

The Timed Up and Go (TUG) test was used to evaluate the risk of falls [17]. Participants were instructed to stand up from an armchair, walk 3 m, and then return to sit down. The completion time (seconds) was recorded from standing up to sitting down. A high TUG time, which is greater than 12 s was defined as having a high risk of falls [18].

A comprehensive questionnaire was used to collect demographic and lifestyle characteristics data containing age, sex, smoking habits, alcohol consumption, and physical activity. Height was obtained through physical examinations. Current smoking was defined as the use of at least one cigarette every 1–3 days in the past six months. Current alcohol drinking was defined as drinking at least three times per week in the past six months. Physical activity was defined by the frequency of exercise during the past year, including "never", "1–3 times per month", "1–2 times per week", "3–5 times per week", and "6–7 times per month". We categorized physical activity into "no exercise" and "exercise" by classifying "1–3 times per month", "1–2 times per week", "3–5 times per week", and "6–7 times per month" into the "exercise" group and incorporated it as a binary variable in our models. The definitions of medical history, including hypertension, diabetes, and hyperlipidemia, have been previously described [19].

2.3. Statistical analysis

The characteristics of participants were described as mean (standard deviation, SD) or frequencies (%) as appropriate. The normality of continuous variables was evaluated by the Shapiro-Wilk test, and the homogeneity of variance by Levene's test. Since the symmetry and variability gait data presented skewness, logarithmic transformation and square root transformation was applied respectively. Differences between participants with and without prevalent CKD were examined using two-sample t-tests or Wilcoxon rank sum tests for continuous variables and Pearson's chi-squared tests or Fisher's exact tests for categorical variables.

Considering the strong correlation of these fifteen quantitative gait parameters, factor analysis was performed to categorize them into independent gait domains using the principal component method with varimax rotation based on a prior study [19]. To represent poorer gait performances with lower values, the original variables in the rhythm, symmetry, variability, and phase domains were inverted before. The independent factors were standardized and expressed as z-scores for further analysis.

The association between prevalent CKD and the high TUG time was evaluated using binary logistic regression models. Associations of prevalent CKD with quantitative gait markers and gait domains were investigated using general linear regression models. The regression analysis was fitted in two models: Model 1 was adjusted for age, sex, and height; Model 2 was further adjusted for hypertension, diabetes, hyperlipidemia, smoking, alcohol consumption, and physical activity. The results of general linear regression were shown as standardized beta coefficients. Multiple testing problem was corrected by the false discovery rate (FDR) method. We additionally performed a power analysis to assess the statistical power in our study using the R package "pwr".

A causal mediation analysis was used to determine whether gait parameters mediated the association of prevalent CKD with the high TUG time. The mediation analysis was conducted using the R package "mediation" with 1,000 repetitions. We estimated the direct effect c' (the direct effect of prevalent CKD on the high TUG time), the mediation effect a*b (a, the effect of prevalent CKD on gait markers; b, the effect of gait markers on the high TUG time), and the total effect c (c = direct effect c'+indirect effect a*b). If c is significant while c' is not, it indicates that the independent variable has a significant impact on the dependent variable without the consideration of the mediating variable. However, when the mediating variable is taken into account, the influence of the independent variable on the dependent variable becomes insignificant, suggesting that a complete mediation is present. If both c and c' are significant, it means that the independent variable significantly affects the dependent variable, and even after considering the mediating variable, the independent variable still has a significant direct effect on the dependent variable, indicating that there is a partial mediation [20].

To mitigate differences in sample size between prevalent CKD participants and non-CKD participants, we employed a 1:2 ratio propensity score matching (PSM) analysis as a sensitivity analysis. Variables, including sex, diabetes, and physical activity were used to match to minimize the impact of unbalanced potential confounding factors and make each standardized mean difference (SMD) < 0.1, which is considered negligible. The threshold of statistical significance was set at corrected $P < 0.05$. Statistical analyses were

performed using R software (Version 4.2.2).

3. Results

3.1. Participant characteristics

Seventy-two (11.4 %) of the 634 participants in our study had prevalent CKD. Participants with prevalent CKD were more likely to have diabetes and exhibit longer time of TUG test. They also showed worse spatiotemporal gait performances, including less time in the swing phase, and greater time in double support (Table 1).

3.2. Prevalent CKD and the TUG time

The association between prevalent CKD and the high TUG time is presented in Table 2. In the basic model (adjusted for age, sex, and height), prevalent CKD was associated with a higher TUG time (OR: 1.95, 95%CI: 1.04 to 3.50). The association remained significant after adjusting for cardiovascular risk factors (OR: 2.02, 95%CI: 1.07 to 3.67).

3.3. Prevalent CKD and individual quantitative gait markers

Fig. S2 shows the associations of prevalent CKD with individual quantitative gait parameters. After full adjustment, prevalent CKD was associated with significant abnormalities in the percent of the gait cycle in the swing and double-support phases (both FDR = 0.027). Prevalent CKD was associated with less time in the swing phase of the gait cycle (standardized $\beta = -0.365$, 95%CI: 0.610 to −0.119) and longer time in the double-support phase (standardized $\beta = 0.367$, 95%CI: 0.122 to 0.613).

3.4. Prevalent CKD and gait domains

Quantitative gait parameters were summarized into five independent domains with factor analysis, which accounted for 89.2 % of

Table 1
Characteristics of study participants by CKD status.

Variable	Total, n = 634	No CKD, n = 562	Prevalent CKD, n = 72	*P*
Female, n (%)	374 (59.0)	331 (58.9)	43 (59.7)	0.995
Age, y	59.8 (2.9)	59.8 (2.9)	59.9 (3.1)	0.987
Height, cm	159.08 (7.83)	159.15 (7.78)	158.60 (8.26)	0.574
Current smoker, n (%)	80 (12.6)	68 (12.1)	12 (16.9)	0.338
Alcohol consumption, n (%)	173 (27.3)	153 (27.2)	20 (27.8)	1.000
Physical activity, n (%)				0.357
Never	536 (84.5)	474 (74.8)	62 (9.8)	
1–3 times/month	6 (0.9)	4 (0.6)	2 (0.3)	
1–2 times/week	22 (3.5)	19 (3.0)	3 (0.5)	
3–5 times/week	25 (3.9)	23 (3.6)	2 (0.3)	
6–7 times/month	45 (7.1)	42 (6.6)	3 (0.5)	
Hypertension, n (%)	344 (55.6)	299 (54.7)	45 (62.5)	0.258
Hyperlipidemia, n (%)	365 (57.6)	322 (57.3)	43 (59.7)	0.791
Diabetes, n (%)	68 (10.7)	53 (9.4)	15 (20.8)	**0.006**
eGFR, ml/min/1.73 m^2	88.67 (24.95)	93.46 (22.12)	51.25 (9.07)	**<0.001**
TUG test, s	10.38 (2.53)	10.27 (2.41)	11.22 (3.23)	**0.003**
TUG>12s, n (%)	92 (14.5)	75 (13.3)	17 (23.6)	**0.031**
Gait parameters				
Stride time, s	1.05 (0.13)	1.04 (0.13)	1.05 (0.08)	0.595
Swing time, s	0.36 (0.04)	0.36 (0.04)	0.36 (0.03)	0.395
Stance time, s	0.68 (0.08)	0.68 (0.08)	0.69 (0.06)	0.132
Stance time symmetry	1.02 (0.06)	1.03 (0.06)	1.02 (0.02)	0.701
Swing time symmetry	1.05 (0.10)	1.05 (0.10)	1.04 (0.04)	0.779
Stride time symmetry	1.02 (0.07)	1.02 (0.07)	1.01 (0.01)	0.354
Stance time CV, %	3.14 (3.71)	3.18 (3.91)	2.76 (1.21)	0.506
Swing time CV, %	3.84 (4.91)	3.90 (5.17)	3.38 (1.79)	0.506
Stride time CV, %	2.48 (3.19)	2.51 (3.37)	2.28 (1.18)	0.800
Swing time (%GC), %	35.14 (2.26)	35.23 (2.26)	34.41 (2.13)	**0.004**
Double support time (%GC), %	30.14 (4.53)	29.96 (4.54)	31.58 (4.15)	**0.004**
Stride length, m	1.16 (0.17)	1.16 (0.17)	1.16 (0.17)	0.865
Maximum swing velocity, m/s	3.87 (0.54)	3.87 (0.55)	3.86 (0.53)	0.774
Heel strike angle, °	7.19 (6.82)	6.99 (6.82)	8.76 (6.67)	**0.038**
Gait velocity, m/s	1.08 (0.16)	1.08 (0.16)	1.10 (0.15)	0.564

Notes: Categorical variables are presented as numbers (percentages), and continuous variables as means (SDs).
Abbreviation: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TUG, Timed-Up-and-Go; CV, coefficient of variation; %GC, percentage of the gait cycle.

Table 2
The association of prevalent and the high TUG time.

	Model	TUG >12s		
		OR	95 % CI	***P***
Prevalent CKD	Model 1	1.95	(1.04,3.50)	**0.030**
	Model 2	2.02	(1.07,3.67)	**0.025**

Model 1 was adjusted for sex, age, and height; Model 2 was further adjusted for hypertension, diabetes, hyperlipidemia, smoking, alcohol consumption, and physical activity.
Abbreviation: CKD, chronic kidney disease; TUG, Timed-Up-and-Go; OR, odds ratio; 95 % CI, 95 % confidence interval.

the total variance (Table S2). Referring to previous studies [9,21,22], we categorized them as rhythm domain (stride time, stance time, swing time), phase domain (double support time percentage of the gait cycle, swing time percentage of the gait cycle), symmetry domain (stance time percentage of the gait cycle symmetry, swing time percentage of the gait cycle symmetry, stride time symmetry), variability domain (stance time coefficient of variation, swing time coefficient of variation, stride time coefficient of variation), and pace domain (stride length, maximum swing velocity, heel strike angle, gait velocity). Table 3 shows the associations of prevalent CKD with gait domains. After full adjustment, prevalent CKD was associated with poorer performance in the phase domain (standardized $\beta = -0.391$, 95 % CI: 0.636 to −0.146). There were no significant associations between prevalent CKD and other gait domains.

3.5. Prevalent CKD, gait markers and the TUG time

Mediation analysis was used to determine whether these identified quantitative gait abnormalities could explain a higher TUG time in participants with prevalent CKD. We found that the association of prevalent CKD with the high TUG time was completely mediated by time in the swing and double support phases of the gait cycle, which manifested the performance in the phase domain (Fig. 1 A - C and Table S3). The mediating effects of the swing time (%GC) and double support time (%GC) accounted for 31.6 % and 29.6 % ($P_{mediation} = 0.044$ and 0.042, respectively), and the effect of the performance in the phase domain for 26.9 % ($P_{mediation} = 0.048$).

3.6. Stratified analysis by eGFR levels

We further investigated the associations between different stages of CKD and the high TUG time as well as quantitative gait performance. According to CKD severity, participants were classified into four groups, of which the proportions were 45.7 % (eGFR ≥90, N = 290), 42.9 % (60 ≤ eGFR <90, N = 272), and 10.8 % (30 ≤ eGFR <59, N = 69), respectively. The associations between CKD stages and the TUG time were examined (Table S4). Compared with stage 1, stage 3 showed a significantly higher TUG time after full adjustment (OR: 2.13, 95%CI: 1.06 to 4.15). We also observed a trend ($P = 0.047$) across different groups, indicating that participants with severer CKD may exhibit a higher TUG time when walking. Tables S5 and S6 exhibited the associations between CKD stages and their gait features. Participants with stage 3 CKD had less time in the swing phase of the gait cycle (standardized $\beta = -0.481$, 95%CI: 0.743 to −0.219), longer time in the double-support phase (standardized $\beta = 0.488$, 95%CI: 0.225 to 0.750), and larger heel strike angle (standardized $\beta = 0.370$, 95%CI: 0.112 to 0.628). In addition to the above three individual gait parameters, longer stance time also had a linear trend with CKD stages. Among gait domains, stage 3 CKD was associated with poorer performance in the phase domain (standardized $\beta = -0.535$, 95 % CI: 0.796 to −0.274). And, participants with severer CKD may exhibit linear trends in rhythm, variability, and phase domain (*P* for trend<0.05).

Table 3
Associations of prevalent CKD with gait domains.

Gait domains	Model	Prevalent CKD		
		β (95%CI)	*P*	*P* (FDR)
Rhythm	Model 1	−0.100 (−0.321,0.120)	0.371	0.572
	Model 2	−0.096 (−0.320,0.128)	0.401	0.668
Symmetry	Model 1	0.018 (−0.231,0.267)	0.887	0.887
	Model 2	0.017 (−0.236,0.270)	0.896	0.896
Variability	Model 1	0.089 (−0.146,0.323)	0.457	0.572
	Model 2	0.071 (−0.168,0.309)	0.560	0.700
Phase	Model 1	−0.382 (−0.623,-0.141)	0.002	**0.010**
	Model 2	−0.391 (−0.636,-0.146)	0.002	**0.009**
Pace	Model 1	0.162 (−0.074,0.397)	0.178	0.444
	Model 2	0.155 (−0.081,0.390)	0.197	0.494

Notes: Values are estimated coefficients (95%CI). Model 1 was adjusted for sex, age, and height; Model 2 was further adjusted for hypertension, diabetes, hyperlipidemia, smoking, alcohol consumption, and physical activity.
Abbreviations: CKD, chronic kidney disease; 95 % CI, 95 % confidence interval; FDR, false discovery rate.

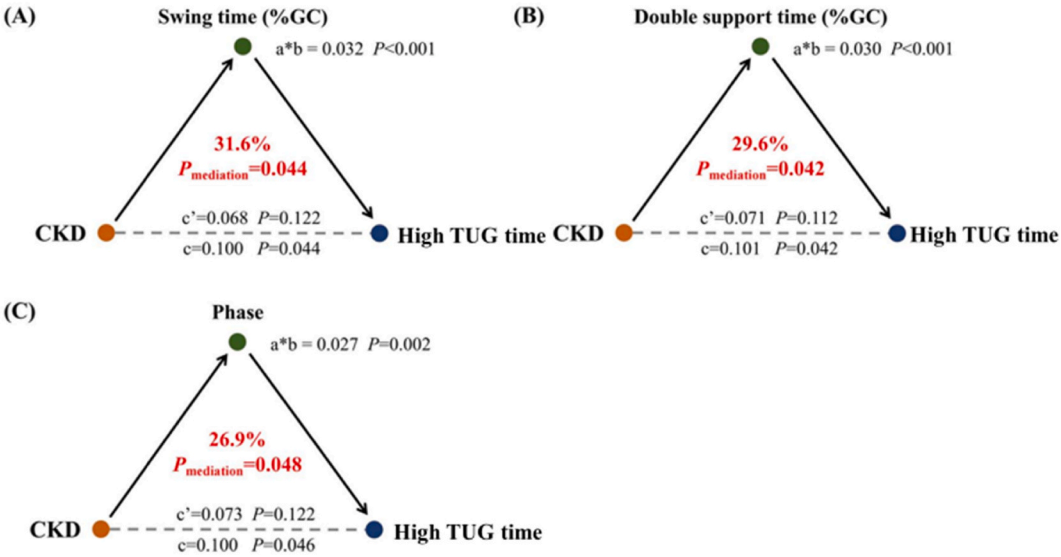

Fig. 1. Mediation effects of gait markers in the associations between prevalent CKD and fall risk (All models were adjusted for sex, age, height, hypertension, diabetes, hyperlipidemia, smoking, alcohol consumption, and physical activity. CKD, chronic kidney disease; %GC, percentage of the gait cycle; a, the effect of prevalent CKD on gait markers; b, the effect of gait markers on the risk of falls; a*b, the mediation effect; c', the direct effect of prevalentCKD on the risk of falls; c, the total effect of prevalent CKD on the risk of falls.).

3.7. Propensity score matching analysis

The characteristics of 144 participants in the control group and 72 participants in the prevalent CKD group were effectively balanced (Table S7). And the SMD of each covariate between the two groups was negligible (<0.1). After PSM, prevalent CKD participants continued to exhibit a higher TUG time (OR: 2.16, 95%CI: 1.01 to 4.63) (Table S8). And they still showed poorer performance in the phase domain (standardized $\beta = -0.391$, 95 % CI: 0.662 to −0.119), including less time in the swing phase of the gait cycle (standardized $\beta = -0.392$, 95%CI: 0.653 to −0.131) and longer time in the double-support phase (standardized $\beta = 0.408$, 95%CI: 0.155 to 0.661). Even after full adjustment, the above associations we found retained significant (Tables S9 and S10).

4. Discussion

Among community-dwelling 55-65 adults, we observed a higher TUG time in people with prevalent CKD than those without. They exhibited worse gait performance in the phase domain, including time spent in the swing and double support phases of the gait cycle, which could explain their higher TUG time. Our findings suggest that abnormal gait signs in the phase domain might be potential markers to detect individuals with CKD at a higher TUG time.

In our study, there was no significant association between CKD status and gait speed, which is different from other cohort studies [11,23]. The possible explanations for our findings could be as follows: the small sample size of our study, the relatively younger overall age, and the milder conditions of the participants. Our results may indeed support that gait parameters related to phase are sensitive indicators of gait impairment. Phase covers several quantitative gait parameters associated with the temporal aspects of gait [9,10], potentially being more sensitive to changes in gait. The gait domains are capable of detecting alterations within the gait cycle [24] that may not be readily apparent in single gait parameter. Given that the parameters within the phase can reflect subtle differences in gait at the early stage, they may demonstrate abnormalities before any significant decline in gait speed.

Prior research has revealed that kidney dysfunction was associated with falls and physical performance limitations, such as muscle function and mobility [10,11,25,26]. In the Rotterdam Study, the investigators showed that worse kidney function evaluated by eGFR or albumin-to-creatinine ratio (ACR) is associated with a higher risk of self-reported falls [10]. The Health, Aging and Body Composition (Health ABC) Study, including participants aged 70–79, found that higher cystatin C level is associated with worse performance on physical function tested by 400-m walk, extremity performance, and grip and knee extension strength [27]. Several functional mobility tests have been proven effective in identifying individuals at high fall risk, among which the TUG test was the most frequently assessed single test [28]. Consistently, we found that kidney dysfunction is associated with a higher risk of falls (as defined by TUG).

In alignment with previous studies [8,23,29], we found that CKD individuals exhibited worse gait performance. However, a recent systematic review noted the dearth of studies investigating spatiotemporal gait characteristics in patients with CKD (7). Our study used a validated wearable insole-like device to collect spatiotemporal gait parameters and then extracted independent domains from vast individual gait variables with factor analysis. Among all the gait domains, we only found the phase domain (including the swing and double-support phases) to be significantly related to kidney function. Similarly, the Central Control of Mobility in Aging (CCMA) study

showed that the rhythm domain (including the swing phase, stance phase, double support phase, and step length) was associated with eGFR among participants with CKD (23). In the Rotterdam Study, eGFR was only associated with the variability domain (including the variability in step length and stance time), and ACR was additionally associated with slower scores in the pace domain (including step length and velocity) and phase domain (including single-support phase only) [10]. In general, we could detect various spatiotemporal gait abnormalities among CKD individuals based on quantitative measurements. However, there were also several differences in these results, which may be partly due to the different gait parameters collected or defined, the different indicators chosen to represent kidney function, and disparities in the characteristics of participants.

The abnormal gait characteristics in the phase domain that we identified to be associated with CKD have been proven to be specifically related to a higher risk of falls [6]. Given that people with kidney dysfunction experience a higher TUG time, spatiotemporal gait abnormalities could be considered potential markers to detect them. Based on mediation analysis, we found that the association of prevalent CKD with high TUG time was completely mediated by time in the swing and double-support phases of the gait cycle, which manifested poor performance in the phase domain. Hence, quantitative gait assessment might be a potential screening tool for 55-65 adults with CKD in need of fall prevention.

Several limitations of this study should be acknowledged. First, our results are based on cross-sectional data, which makes it difficult for us to obtain longitudinal changes in gait. Therefore, the causal relationship between CKD and gait characteristics is hard to determine. Secondly, our population was relatively healthier and younger and showed a lower prevalence of CKD as well as milder kidney dysfunction according to the value of eGFR. Thus, people with later-stage CKD are under-represented in our study. However, we performed a power analysis to assess the statistical power. The minimum power value in our study was 0.76, which showed that our analysis had guaranteed sufficient power to detect the effect we're investigating, although with a relatively small sample size. Notably, our findings indicate that subtle gait abnormalities could be detected even among mild CKD individuals, revealing its screening value to fall prevention. Thirdly, CKD was defined by the baseline cystatin C levels, while a single measurement may be limited in reflecting true situations because of its variability over time. Fourthly, information on inflammation and metabolic factors, musculoskeletal factors, and neurological factors were not taken into account, which may cause residual confounding. Nonetheless, this study was based on TIS, which excluded individuals with diagnosed circulatory, neurological, psychiatric, or endocrinological diseases. Fifthly, we did not considerate the cognitive impairment factors because individuals with neuropsychiatric diseases have been excluded at baseline. However, studies have demonstrated that cognitive impairment significantly influence the risk of falls [30,31], it could be beneficial to explore whether cognitive domains related to executive functions have an impact on the association in subsequent research. Finally, causal conclusions cannot be drawn in this mediation analysis on the basis of a cross-sectional study. However, we evaluated the risk of falls by the TUG test instead of fall incidents and excluded those with a history of fractures that might be caused by falls. To some extent, it can reduce the possibility of reverse causality that falls result in gait abnormalities.

5. Conclusion

The present study indicates that prevalent CKD is associated with a higher TUG time and worse performance in quantitative spatiotemporal gait indicators and gait patterns. Quantitative gait markers in the phase domain, including the swing and double-support phases, are mediators of prevalent CKD and high TUG time in 55–65 adults. Our findings suggest that even mild CKD individuals exhibit subtle gait impairments, which may increase the TUG time. Future studies should investigate the predictive value of spatiotemporal gait markers to falls at each stage of kidney dysfunction, improving the quality of life in CKD.

Ethics approval

The Taizhou Imaging Study was approved by the Ethics Committee of the School of Life Sciences, Fudan University, Shanghai, China (Institutional Review Board Approval No. 496) and Fudan University Taizhou Institute of Health Sciences (Institutional Review Board Approval No. B017). This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent

Informed consent was obtained from all individual participants included in the study.

Funding

This work was supported by the Science and Technology Innovation 2030 Major Projects (grant number: 2022ZD0211600), the National Natural Science Foundation of China (grant number: 82304239), Natural Science Foundation of Shanghai, China (grant numbers: 23ZR1414000), Key Research and Development Plans of Jiangsu Province, China (grant number: BE2021696), the National Key Research and Development program of China (grant number: 2021YFC2500100), Fudan School of Public Health-Jiading CDC key disciplines for the high-quality development of public health (grant number: GWGZLXK-2023-02).

Data availability statement

The data associated with our study has not been deposited into a publicly available repository. Data will be made available on

request.

CRediT authorship contribution statement

Xin Zhang: Writing – original draft, Visualization, Formal analysis, Conceptualization. **Hao Wang:** Writing – original draft. **Heyang Lu:** Investigation. **Min Fan:** Supervision, Project administration. **Weizhong Tian:** Supervision, Project administration. **Yingzhe Wang:** Supervision, Project administration. **Mei Cui:** Supervision, Project administration. **Yanfeng Jiang:** Supervision, Project administration. **Chen Suo:** Supervision, Project administration. **Tiejun Zhang:** Supervision, Project administration. **Li Jin:** Supervision, Project administration. **Kelin Xu:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Xingdong Chen:** Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We appreciate all the participants, staffs, and graduate students of TIS for their crucial contributions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35292.

References

[1] GBD Chronic Kidney Disease Collaboration, Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017, Lancet 395 (10225) (2020) 709–733, https://doi.org/10.1016/s0140-6736(20)30045-3.
[2] T.K. Chen, D.H. Knicely, M.E. Grams, Chronic kidney disease diagnosis and management: a review, JAMA 322 (13) (2019) 1294–1304, https://doi.org/10.1001/jama.2019.14745.
[3] L. Zhang, F. Wang, L. Wang, W. Wang, B. Liu, J. Liu, et al., Prevalence of chronic kidney disease in China: a cross-sectional survey, Lancet 379 (9818) (2012) 815–822, https://doi.org/10.1016/s0140-6736(12)60033-6.
[4] N.A. Goto, A.C.G. Weststrate, F.M. Oosterlaan, M.C. Verhaar, H.C. Willems, M.H. Emmelot-Vonk, et al., The association between chronic kidney disease, falls, and fractures: a systematic review and meta-analysis, Osteoporos. Int. 31 (1) (2020) 13–29, https://doi.org/10.1007/s00198-019-05190-5.
[5] V.J. Verlinden, J.N. van der Geest, J. Heeringa, A. Hofman, M.A. Ikram, Gait shows a sex-specific pattern of associations with daily functioning in a community-dwelling population of older people, Gait Posture 41 (1) (2015) 119–124, https://doi.org/10.1016/j.gaitpost.2014.09.003.
[6] J. Verghese, R. Holtzer, R.B. Lipton, C. Wang, Quantitative gait markers and incident fall risk in older adults, J Gerontol A Biol Sci Med Sci 64 (8) (2009) 896–901, https://doi.org/10.1093/gerona/glp033.
[7] D.D. Zemp, O. Giannini, P. Quadri, E.D. de Bruin, Gait characteristics of CKD patients: a systematic review, BMC Nephrol. 20 (1) (2019) 83, https://doi.org/10.1186/s12882-019-1270-9.
[8] D.D. Zemp, O. Giannini, P. Quadri, M. Rabuffetti, M. Tettamanti, E.D. de Bruin, Gait disorders in CKD patients: muscle wasting or cognitive impairment? A cross-sectional pilot study to investigate gait signatures in Stage 1-5 CKD patients, BMC Nephrol. 23 (1) (2022) 72, https://doi.org/10.1186/s12882-022-02697-8.
[9] J.H. Hollman, E.M. McDade, R.C. Petersen, Normative spatiotemporal gait parameters in older adults, Gait Posture 34 (1) (2011) 111–118, https://doi.org/10.1016/j.gaitpost.2011.03.024.
[10] S. Sedaghat, S.K.L. Darweesh, V.J.A. Verlinden, J.N. van der Geest, A. Dehghan, O.H. Franco, et al., Kidney function, gait pattern and fall in the general population: a cohort study, Nephrol. Dial. Transplant. 33 (12) (2018) 2165–2172, https://doi.org/10.1093/ndt/gfy043.
[11] J. Tran, E. Ayers, J. Verghese, M.K. Abramowitz, Gait abnormalities and the risk of falls in CKD, Clin. J. Am. Soc. Nephrol. 14 (7) (2019) 983–993, https://doi.org/10.2215/cjn.13871118.
[12] Y. Jiang, M. Cui, W. Tian, S. Zhu, J. Chen, C. Suo, et al., Lifestyle, multi-omics features, and preclinical dementia among Chinese: the Taizhou Imaging Study, Alzheimers Dement 17 (1) (2021) 18–28, https://doi.org/10.1002/alz.12171.
[13] L.A. Inker, C.H. Schmid, H. Tighiouart, J.H. Eckfeldt, H.I. Feldman, T. Greene, et al., Estimating glomerular filtration rate from serum creatinine and cystatin C, N. Engl. J. Med. 367 (1) (2012) 20–29, https://doi.org/10.1056/NEJMoa1114248.
[14] A.C. Baxmann, M.S. Ahmed, N.C. Marques, V.B. Menon, A.B. Pereira, G.M. Kirsztajn, et al., Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C, Clin. J. Am. Soc. Nephrol. 3 (2) (2008) 348–354, https://doi.org/10.2215/cjn.02870707.
[15] P.E. Stevens, A. Levin, Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline, Ann. Intern. Med. 158 (11) (2013) 825–830, https://doi.org/10.7326/0003-4819-158-11-201306040-00007.
[16] Z. Yang, F. Lin, W. Xu, J. Langan, L. Cavuoto, Z. Li, et al. (Eds.), Validation of a Novel Gait Analysis System, Connected Health, 2017.
[17] A. Shumway-Cook, S. Brauer, M. Woollacott, Predicting the probability for falls in community-dwelling older adults using the Timed up & Go Test, Phys. Ther. 80 (9) (2000) 896–903.
[18] R.B. Chow, A. Lee, B.G. Kane, J.L. Jacoby, R.D. Barraco, S.W. Dusza, et al., Effectiveness of the "Timed up and Go" (TUG) and the Chair test as screening tools for geriatric fall risk assessment in the ED, Am. J. Emerg. Med. 37 (3) (2019) 457–460, https://doi.org/10.1016/j.ajem.2018.06.015.
[19] Y. Wang, Y. Jiang, H. Lu, W. Tian, P. Li, K. Xu, et al., Cross-sectional associations between cortical thickness and independent gait domains in older adults, J. Am. Geriatr. Soc. 70 (9) (2022) 2610–2620, https://doi.org/10.1111/jgs.17840.
[20] D.P. MacKinnon, A.J. Fairchild, M.S. Fritz, Mediation analysis, Annu. Rev. Psychol. 58 (2007) 593–614, https://doi.org/10.1146/annurev.psych.58.110405.085542.
[21] S.K.L. Darweesh, S. Licher, F.J. Wolters, P.J. Koudstaal, M.K. Ikram, M.A. Ikram, Quantitative gait, cognitive decline, and incident dementia: the Rotterdam Study, Alzheimers Dement 15 (10) (2019) 1264–1273, https://doi.org/10.1016/j.jalz.2019.03.013.

[22] V.J. Verlinden, J.N. van der Geest, Y.Y. Hoogendam, A. Hofman, M.M. Breteler, M.A. Ikram, Gait patterns in a community-dwelling population aged 50 years and older, Gait Posture 37 (4) (2013) 500–505, https://doi.org/10.1016/j.gaitpost.2012.09.005.
[23] J.Q. Ho, J. Verghese, M.K. Abramowitz, Walking while talking in older adults with chronic kidney disease, Clin. J. Am. Soc. Nephrol. 15 (5) (2020) 665–672, https://doi.org/10.2215/cjn.12401019.
[24] Q. Duan, Y. Zhang, W. Zhuang, W. Li, J. He, Z. Wang, et al., Gait domains may Be used as an auxiliary diagnostic index for Alzheimer's disease, Brain Sci. 13 (11) (2023), https://doi.org/10.3390/brainsci13111599.
[25] S. Anand, K.L. Johansen, M. Kurella Tamura, Aging and chronic kidney disease: the impact on physical function and cognition, J Gerontol A Biol Sci Med Sci 69 (3) (2014) 315–322, https://doi.org/10.1093/gerona/glt109.
[26] P. Painter, R.L. Marcus, Assessing physical function and physical activity in patients with CKD, Clin. J. Am. Soc. Nephrol. 8 (5) (2013) 861–872, https://doi.org/10.2215/cjn.06590712.
[27] M.C. Odden, G.M. Chertow, L.F. Fried, A.B. Newman, S. Connelly, S. Angleman, et al., Cystatin C and measures of physical function in elderly adults: the health, aging, and Body composition (HABC) study, Am. J. Epidemiol. 164 (12) (2006) 1180–1189, https://doi.org/10.1093/aje/kwj333.
[28] Jepsen D. Beck, K. Robinson, G. Ogliari, M. Montero-Odasso, N. Kamkar, J. Ryg, et al., Predicting falls in older adults: an umbrella review of instruments assessing gait, balance, and functional mobility, BMC Geriatr. 22 (1) (2022) 615, https://doi.org/10.1186/s12877-022-03271-5.
[29] C.K. Liu, A. Lyass, J.M. Massaro, Sr. D'Agostino Rb, C.S. Fox, J.M. Murabito, Chronic kidney disease defined by cystatin C predicts mobility disability and changes in gait speed: the Framingham Offspring Study, J Gerontol A Biol Sci Med Sci 69 (3) (2014) 301–307, https://doi.org/10.1093/gerona/glt096.
[30] K. Delbaere, N.A. Kochan, J.C. Close, J.C. Menant, D.L. Sturnieks, H. Brodaty, et al., Mild cognitive impairment as a predictor of falls in community-dwelling older people, Am. J. Geriatr. Psychiatr. 20 (10) (2012) 845–853, https://doi.org/10.1097/JGP.0b013e31824afbc4.
[31] R. Dubbioso, M. Spisto, J.M. Hausdorff, G. Aceto, V.V. Iuzzolino, G. Senerchia, et al., Cognitive impairment is associated with gait variability and fall risk in amyotrophic lateral sclerosis, Eur. J. Neurol. 30 (10) (2023) 3056–3067, https://doi.org/10.1111/ene.15936.