

Gait and balance in apolipoprotein $\epsilon 4$ allele carriers in older adults and Parkinson's disease

Rosie Morris^{a,b}, Douglas N. Martini^{a,c}, Valerie E. Kelly^d, Katrijn Smulders^e, Katrina Ramsey^f, Amie Hiller^{a,g}, Kathryn A. Chung^{a,g}, Shu-Ching Hu^{h,i}, Cyrus P. Zabetian^{h,i}, Kathleen L. Poston^j, Ignacio F. Mata^{h,i,k}, Karen L. Edwards^l, Jodi Lapidus^f, Brenna Cholerton^m, Thomas J. Montine^m, Joseph F. Quinn^{a,g}, Fay Horak^{a,g,n,o,*}

^a Department of Neurology, Oregon Health and Science University, Portland, OR, USA

^b Department of Sport, Exercise and Rehabilitation, Northumbria University, Newcastle-upon-Tyne, UK

^c Department of Kinesiology, University of Massachusetts Amherst, Amherst, MA, USA

^d Department of Rehabilitation Medicine, University of Washington School of Medicine, Seattle, WA, USA

^e Sint Maartenskliniek Research Department, Nijmegen, the Netherlands

^f School of Public Health, Oregon Health and Science University, Portland, OR, USA

^g Department of Rehabilitation Medicine, University of Washington School of Medicine, Seattle, WA, USA

^h Sint Maartenskliniek Research Department, Nijmegen, the Netherlands

ⁱ Portland Veterans Affairs Health Care System, Portland, OR, USA

^j Department of Neurology, University of Washington School of Medicine, Seattle, WA, USA

^k Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA

^l Department of Neurology and Neurological Sciences, Stanford School of Medicine, Palo Alto, CA, US

^m Lerner Research Institute, Genomic Medicine, Cleveland Clinic Foundation, Cleveland, OH, USA

ⁿ Department of Epidemiology and Biostatistics, University of California, Irvine, CA, USA

^o Department of Pathology, Stanford University School of Medicine, Palo Alto, CA, USA

ARTICLE INFO

Keywords:

Gait
Balance
Older adults
Parkinson's disease
APOE

ABSTRACT

Background: Gait and balance impairments are among the most troublesome and heterogeneous in Parkinson's disease (PD). This heterogeneity may, in part, reflect genetic variation. The apolipoprotein E (APOE) gene has three major allelic variants ($\epsilon 2$, $\epsilon 3$ and $\epsilon 4$). Previous work has demonstrated that older adult (OA) APOE $\epsilon 4$ carriers demonstrate gait deficits. This study compared gait and balance measures between APOE $\epsilon 4$ carriers and non-carriers in both OA and PD.

Methods: 334 people with PD (81 APOE $\epsilon 4$ carriers and 253 non-carriers) and 144 OA (41 carriers and 103 non-carriers) were recruited. Gait and balance were assessed using body-worn inertial sensors. Two-way analyses of covariance (ANCOVA) compared gait and balance characteristics between APOE $\epsilon 4$ carriers and non-carriers in people with PD and OA, controlling for age, gender, and testing site.

Results: Gait and balance were worse in people with PD compared to OA. However, there were no differences between APOE $\epsilon 4$ carriers and non-carriers in either the OA or PD group. In addition, there were no significant group (OA/PD) by APOE $\epsilon 4$ status (carrier/non-carrier) interaction effects for any measures of gait or balance. **Conclusions:** Although we found expected impairments in gait and balance in PD compared to OA, gait and balance characteristics did not differ between APOE $\epsilon 4$ carriers and non-carriers in either group. While APOE status did not impact gait and balance in this cross-sectional study, future work is needed to determine whether progression of gait and balance deficits is faster in PD APOE $\epsilon 4$ carriers.

* Corresponding author at: Department of Neurology, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA.

E-mail address: horakf@ohsu.edu (F. Horak).

<https://doi.org/10.1016/j.prdoa.2023.100201>

Received 7 September 2022; Received in revised form 9 March 2023; Accepted 14 May 2023

Available online 17 May 2023

2590-1125/© 2023 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder for which gait and balance deficits are some of the most troublesome motor symptoms. Gait and balance impairments respond poorly to current treatment options and therefore novel treatment targets are needed [1]. Gait and balance deficits demonstrate heterogeneity across patients. Heterogeneity in gait and balance may be due, in part, to genetic variation which could drive differences in pathophysiology and impact disease diagnosis and progression [2]. Further understanding of heterogeneity would provide a more accurate prediction of disease trajectory for individual patients and therefore provide a personalized medicine approach for rehabilitation.

The apolipoprotein E (*APOE*) gene has three major allelic variants ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$) and the *APOE* $\epsilon 4$ allele is associated with a higher risk and earlier onset of Alzheimer's disease (AD) [3]. Evidence suggests that carriers of the *APOE* $\epsilon 4$ allele have higher cerebral amyloid- β ($A\beta$), a biomarker for AD pathology [3]. In the PD population, *APOE* $\epsilon 4$ allele carriers have a greater risk of cognitive decline and dementia [4,5] with specific impairments of memory encoding and learning and verbal memory [6,7] although this has been disputed by other studies [8]. Pathologically, the *APOE* $\epsilon 4$ allele causes greater $A\beta$ plaques and increased white matter burden with pathological features associated with gait impairment in people with PD [9,10]. Due to the recognized cortical control of gait and balance in PD (i.e., attention and executive function) [11], carriers of the *APOE* $\epsilon 4$ allele with PD may also have poorer gait and balance leading to increased risk of falls and freezing of gait.

Older adult (OA) carriers of the *APOE* $\epsilon 4$ allele have demonstrated poorer gait compared to non-carriers, including gait characteristics of stride length and double support time [12–14]. However, no differences have been observed in balance measures between OA with and without the *APOE* $\epsilon 4$ allele [13]. Other studies of OA *APOE* $\epsilon 4$ allele carriers have demonstrated more rapid decline in gait speed and gait variability [15,16]. Although several studies have suggested motor symptoms are no worse in PD *APOE* $\epsilon 4$ allele carriers [4], objective and comprehensive gait and balance characteristics have not yet been assessed which are likely to be more sensitive to underlying pathophysiology. To date, it remains unknown as to whether PD *APOE* $\epsilon 4$ allele carriers may have more impaired gait and balance compared to OA *APOE* $\epsilon 4$ carriers. Due to concomitant pathology, PD *APOE* $\epsilon 4$ allele carriers may demonstrate a greater impact on gait and balance characteristics over and above OA.

This study examined people with PD and OA to determine differences in balance and gait dysfunction in those *APOE* $\epsilon 4$ allele carriers compared to non-carriers. We hypothesized that those with the *APOE* $\epsilon 4$ allele in OA and, to a greater extent in PD, would demonstrate poorer gait and balance.

2. Methods

2.1. Participants

OA and PD Participants were recruited and enrolled as part of the Pacific Udall Center (PUC) Clinical Core between 2010 and 2020 [17]. Participants were recruited and assessments were completed at three sites: Oregon Health and Science University/Portland VA Medical Center, Portland, OR; University of Washington/VA Puget Sound Health Care System, Seattle, WA; and Stanford University, Palo Alto, CA. Participants were included in the study if they (i) had no history of additional neurological disorders and (ii) were able to stand unsupported for a minimum of 30 s. Additionally, people with PD were recruited if they met the criteria for diagnosis of idiopathic PD using the United Kingdom Parkinson's Disease Society Brain Bank Criteria. PD participants were assessed 'on' dopaminergic medication. All subjects provided informed consent approved by the joint Institutional Review Boards at Oregon Health & Science University, the VA Portland Health Care System,

University of Washington, VA Puget Sound Health Care System and Stanford University, (Stanford University, IRB- 37967).

One goal of the PUC Clinical Core was to assess balance and gait measures in genetic subgroups of OA and PD; therefore, our cohorts were enriched for specific subgroups. The PD cohort was enriched in individuals who carried either a *GBA* variant (including E326K mutation) or *APOE* $\epsilon 4$ allele. All eligible *GBA* variant or *APOE* $\epsilon 4$ carriers in the existing PUC Clinical Core were invited to participate in this study. Those with $\epsilon 2\epsilon 4$ were removed from analysis ($n = 4$), due to the known protective effect of $\epsilon 2$ [18]. As *GBA* variants with PD are known to have worse motor symptoms [19,20], sub-analysis was completed to ensure this did not impact on results. In addition, the OA cohort was enriched for *APOE* $\epsilon 4$ carriers, and all eligible *APOE* $\epsilon 4$ carriers in the PUC cohort were invited to participate.

2.2. Demographic and clinical characteristics

Age, gender, and years of education were recorded for all participants. PD motor severity was assessed using the Movement Disorders Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS III) and the modified Hoehn and Yahr scale (H&Y). For PD medication, daily dopaminergic dose was calculated using the levodopa equivalent daily dose score (LEDD). The Montreal Cognitive Assessment (MoCA) assessed global cognition. Cognitive status was determined via diagnostic consensus conference which were held biweekly using data from a comprehensive neuropsychological battery, clinical assessment, and primary caretaker interviews. Participants were assigned one of the following cognitive diagnostic categories: no cognitive impairment (NCI), mild cognitive impairment (MCI), or dementia, as described previously [17]. All medications were recorded for participants, these can be found in [supplementary Table 1](#).

2.3. Genotyping

Genomic DNA was obtained from peripheral blood or saliva samples using standard procedures. All participants were genotyped for the *APOE* single nucleotide polymorphisms rs429358 and rs7412, which define the $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ alleles, using TaqMan Assays [6]. By design, our cohort was enriched for *GBA* carriers. *GBA* status was determined by screening the entire *GBA* coding region in every participant using Sanger sequencing to capture all known pathogenic mutations (defined as those reported in patients with Gaucher disease [21], and the E326K polymorphism (rs2230288). Here, we use the term *GBA* "variant" to refer to all pathogenic mutations and E326K collectively. All sequencing was performed at a single laboratory at the PUC site in Seattle using methods previously described [22].

2.4. Gait and balance assessment

Participants performed an instrumented gait and balance assessment wearing six inertial sensors (Opal Version 1, APDM Inc., Portland, OR.). Inertial sensors were secured with elastic Velcro straps bilaterally on the wrists and feet as well as at the sternum and fifth lumbar vertebrae. For measurement of gait characteristics, participants were asked to walk at their normal pace back and forth on a straight 7 m walkway in a quiet hallway for two minutes, turning 180 degrees at either end. To assess balance, participants were asked to stand quietly for 60 s, focusing on an image ahead. At the start of each gait and balance trial, a template was used to achieve consistent foot placement (10 cm between left and right heel and 30-degree outward rotation of the feet).

2.5. Gait and balance measures

Measures were selected to represent a comprehensive range of gait and balance domains [23]. For gait, selected characteristics represented domains of pace/turning (gait speed, m/s; stride length, m; foot strike

angle [angle of forefoot at heel strike], deg; turn velocity, deg/s), rhythm (stride time, s; double support, % of gait cycle) and variability (stride length variability, m; stride time variability, s; foot strike angle variability, deg) [24]. The gait analysis via MobilityLab uses sensors on the feet to calculate gait variables during straight walking, excluding gait initiation and steps before and after a turn. Turn velocity was calculated from the sensor on the lumbar spine. The Unscented Kalman Filter was used to fuse information from the accelerometers, gyroscopes, and magnetometers. Gait variables were averaged over the 2-minute walking bout, and all variability measures were measured as the standard deviation.

Balance characteristics were measured as previously described [25] and represented domains of sway area/jerk (jerkiness of sway (jerk) AP and ML, sway dispersion (root mean square, RMS [m/s²]) AP and ML), sway velocity (sway velocity (velocity, [m/s²]) AP and ML), sway frequency antero-posterior (AP) (the highest frequency of sway comprising 95% of the power, derived from acceleration (95 frequency, [Hz]) AP and sway frequency medio-lateral (ML) the highest frequency of sway comprising 95% of the power, derived from acceleration (95 frequency, [Hz]) ML).

2.6. Statistical analyses

Statistical analyses were performed using SPSS V24. Inspection of boxplots and histograms were undertaken to assess data distribution. Several balance characteristics were non-normally distributed and were transformed using natural log to improve normality. First, to determine differences in demographic and clinical data between carriers of at least one APOE ε4 allele and non-carriers for both OA and PD groups, student t-test and chi-square tests were used. A p value of ≤0.05 was used to determine statistical significance.

Two-way analyses of covariance (ANCOVAs) were performed to assess both the effect of group (OA/PD) and APOE ε4 carrier status (carrier/non-carrier), adjusting for age, gender, and testing site. Separate models were used per variable. Significant interactions were then followed up with post hoc comparisons. We further sought to determine the role of cognitive status on group and carrier differences, due to the known impact of APOE ε4 on cognition in both OA and PD. To assess the role of cognitive status, an additional model was analyzed adjusting for cognitive status (NCI, MCI, dementia) in addition to age, gender, and testing site. For all models, a more stringent p value of ≤0.01 to account for multiple comparisons.

A small number of data points were missing (supplementary Table 2). As our cohort was enriched for GBA carriers [20], we also

Table 1
Demographic and Clinical data for OA and PD who are carriers and non-carriers of the APOE ε4 allele. Bold text denotes significant difference.

	Control (All) (n = 144)	PD (All) (n = 334)	Control v's PD p	Control APOE ε4 Non-Carriers (n = 103)	Control APOE ε4 Carriers (n = 41)	Control Carriers v's Non-carriers p	PD APOE ε4Non-Carriers (n = 253)	PD APOE ε4Carriers (n = 81)	PD Carriers v's Non-Carriers p
Age (years)	71.7 (8.0)	68.0 (8.1)	<0.001	71.9 (8.4)	71.3 (7.2)	0.667	68.5 (7.8)	66.1 (8.7)	0.020
Gender M/F	70/74	210/124	0.004	50/53	20/21	0.980	157/96	53/28	0.584
Years of education	17.0 (2.5)	16.5 (2.4)	0.049	16.9 (2.6)	17.1 (2.5)	0.820	16.6 (2.3)	16.3 (2.7)	0.305
MoCA	26.1 (2.6)	25.6 (3.6)	0.167	26.0 (2.6)	26.2 (2.6)	0.824	25.6 (3.5)	25.8 (3.0)	0.611
MDS-UPDRS III	3.0 (3.4)	24.1 (12.2)	<0.001	3.4 (3.7)	2.0 (2.6)	0.037	23.8 (12.2)	25.2 (12.3)	0.374
Hoehn & Yahr n (%)*									0.538
1	NA	15 (4.5%)		NA	NA		12 (5%)	3 (4%)	
1.5	NA	25 (7.5%)		NA	NA		21 (8%)	4 (5%)	
2	NA	213 (63.8)		NA	NA		156 (62%)	57 (70%)	
2.5	NA	56 (16.8)		NA	NA		45 (18%)	11 (14%)	
3	NA	20 (6.0%)		NA	NA		16 (6%)	4 (5%)	
4	NA	4 (1.2%)		NA	NA		2 (1%)	2 (2%)	
APOE Genotype									
ε2ε2				3	0		1	0	
ε2ε3				12	0		51	0	
ε3ε3				88	0		201	0	
ε3ε4				0	36		0	77	
ε4ε4				NA	5		0	4	
LEDD	NA	648.2 (474.3)		NA	NA		641.7 (470.7)	668.9 (488.0)	0.658
Disease duration	NA	7.6 (5.6)		NA	NA		7.5 (5.6)	7.9 (5.7)	0.623
Cognitive status n (%) *			<0.001			0.041			0.459
NCI	91 (64%)	146 (44%)		71 (69%)	20 (50%)		113 (45%)	33 (41%)	
MCI	51 (35%)	157 (47%)		32 (31%)	19 (48%)		119 (47%)	38 (47%)	
Dementia	1 (1%)	30 (9%)		0 (0%)	1 (2%)		20 (8%)	10 (12%)	

Abbreviations: MoCA (Montreal Cognitive Assessment), MDS-UPDRS III (Movement Disorders Society Unified Parkinson's disease Rating Scale), LEDD (Levodopa Equivalent Daily Dose), NCI (no cognitive impairment), MCI (mild cognitive impairment). *cases of missing data, percentages calculated for total group number.

completed a sub-analysis removing those positive for GBA variants to determine if this impacted on our findings.

3. Results

3.1. Demographic and clinical characteristics

Demographic and clinical characteristics for *APOE* ϵ 4 carriers and non-carriers in OA and PD groups are shown in Table 1. In our cohort, the prevalence of *APOE* ϵ 4 was 28.5% in OA and 24.2% in PD, details of the *APOE* allele genotypes are provided in Table 1. Within the OA cohort, a larger proportion of *APOE* ϵ 4 carriers had MCI compared to non-carriers (48% versus 31%, respectively, $p = .041$). Within the PD group, *APOE* ϵ 4 carriers were slightly younger than non-carriers ($p = .020$) but there were no differences for other demographic and clinical data, including disease severity, disease duration, LEDD, and cognitive status. PD participants, both *APOE* ϵ 4 carriers and non-carriers, had mild to moderate motor severity, with approximately half of PD participants having MCI.

3.2. Gait and balance differences between PD and control subjects

Descriptive data for gait and balance characteristics for OA and PD are shown in Table 2. When comparing OA and PD (*APOE* ϵ 4 carriers and non-carriers combined), all characteristics of gait except for stride time and double support time (both rhythm domain) were significantly worse in those with PD (the PD group had slower gait speed, shorter stride length, reduced foot strike angle, slower turn velocity, increased stride length SD, increased foot strike angle SD and increased stride time SD) when controlling for age, gender, and testing site (Fig. 1A). All balance characteristics except for AP Frequency 95% and ML Frequency 95% were significantly different between the OA and PD groups in that those with PD had increased sway area, increased jerkiness of sway (ML and AP), increased sway RMS (ML and AP) and increased sway velocity (ML and AP) (Fig. 1B).

3.3. Gait and balance differences between *APOE* ϵ 4 carriers and non-carriers

Gait characteristics for *APOE* ϵ 4 carriers and non-carriers in the OA and PD groups are shown in Table 3, with box and scatter plots for select gait characteristics shown in Fig. 1A. In both the OA and PD group, no gait differences were found between *APOE* ϵ 4 carriers and non-carriers. In addition, no significant interactions were found between group (OA/PD) and *APOE* ϵ 4 carrier status (carrier/non-carrier) for any of the gait characteristics. When including cognitive status in the model, there were no significant differences for gait characteristics between groups and no significant interaction effect (Table 3). When *GBA* variants ($n = 40$) were removed from analysis, there was still no difference in gait characteristics between PD *APOE* ϵ 4 carriers and non-carriers (see supplementary Table 3).

Balance characteristics for *APOE* ϵ 4 carriers and non-carriers in the OA and PD groups are shown in Table 3, with box and scatter plots for balance characteristics shown in Fig. 1B. No balance differences were found between carriers and non-carriers in either the OA or PD groups. There were no significant group by *APOE* ϵ 4 carrier status interactions for any balance characteristics. When including cognitive status in the model, there were no significant differences for balance characteristics between groups and no significant interaction effect (Table 3). When *GBA* variants ($n = 40$) were removed from analysis, there was still no difference in balance characteristics between PD *APOE* ϵ 4 carriers and non-carriers (see supplementary Table 3).

4. Discussion

This study is the largest to date to assess differences in

Table 2

Gait and Balance differences between all control and PD participants (*APOE* ϵ 4 carriers and non-carriers grouped together). Bold text denotes significant difference.

	Control (All, n = 144)	PD (All, n = 334)	Adjusted Difference p
	Mean (SD)	Mean (SD)	
Gait			
Gait Speed (m/s)	1.05 (0.15)	0.98 (0.19)	<0.001
Stride Length (m)	1.16 (0.14)	1.10 (0.18)	<0.001
Foot Strike Angle (deg)	23.28 (4.95)	19.07 (6.15)	<0.001
Turn Velocity (deg/s)	178.55 (35.26)	152.32 (34.71)	<0.001
Stride Time (s)	1.12 (0.10)	1.14 (0.12)	0.424
Stride Length SD (m)	0.048 (0.023)	0.056 (0.024)	0.004
Foot Strike Angle SD (deg)	2.193 (0.714)	2.537 (0.909)	<0.001
Stride Time SD (s)	0.029 (0.012)	0.040 (0.022)	0.001
Double Support Time (% GCT)	21.82 (3.52)	21.97 (3.89)	0.383
Balance			
Sway Area [†]	0.004 (0.004)	0.014 (0.056)	<0.001
AP Jerk [†]	0.003 (0.004)	0.110 (0.084)	<0.001
ML Jerk [†]	0.001 (0.002)	0.007 (0.046)	<0.001
AP RMS [†] (m/s ²)	0.078 (0.037)	0.101 (0.075)	<0.001
ML RMS [†] (m/s ²)	0.027 (0.017)	0.043 (0.042)	<0.001
AP Velocity [†] (m/ s ²)	0.261 (0.232)	0.359 (0.320)	<0.001
ML Velocity [†] (m/ s ²)	0.108 (0.096)	0.153 (0.145)	<0.001
AP Frequency 95% (Hz)	1.628 (0.405)	1.595 (0.421)	0.785
ML Frequency 95% (Hz)	2.310 (0.517)	2.311 (0.534)	0.816

Adjusted for age, gender, and testing site.

[†] Variables natural log transformed for statistical analysis.

SD = standard deviation, GCT = gait cycle time, AP = anterior-posterior, ML = medio-lateral, RMS = Root Mean Square.

comprehensive gait and balance characteristics in between carriers and non-carriers of the *APOE* ϵ 4 allele in OA and people with PD. Contrary to our hypothesis, we identified no differences in gait or balance measures in either OA or people with PD when comparing carriers versus non-carriers of the *APOE* ϵ 4 allele.

The *APOE* ϵ 4 allele is a major genetic risk factor for MCI and AD [3]. It is also thought that *APOE* ϵ 4 carriers with PD are more susceptible to cognitive decline and dementia over time [26,27], although these findings are not consistent across the literature [8]. Previous findings from our group in a larger cohort of PD found the *APOE* ϵ 4 allele was associated with cognitive impairment across several cognitive domains [6]. Due to the recognized cognitive control of gait and balance [11], we hypothesized that *APOE* ϵ 4 allele carriers would also have more impaired gait and balance than non-carriers. However, our results indicated that this was not the case.

Consistent with our findings, other cross-sectional work assessing gait under single task conditions in OA with no cognitive impairment also detected no differences between carriers versus non-carriers [15]. However, one study in older adults assessing gait under dual-task conditions identified poorer gait in *APOE* ϵ 4 carriers [12], suggesting that

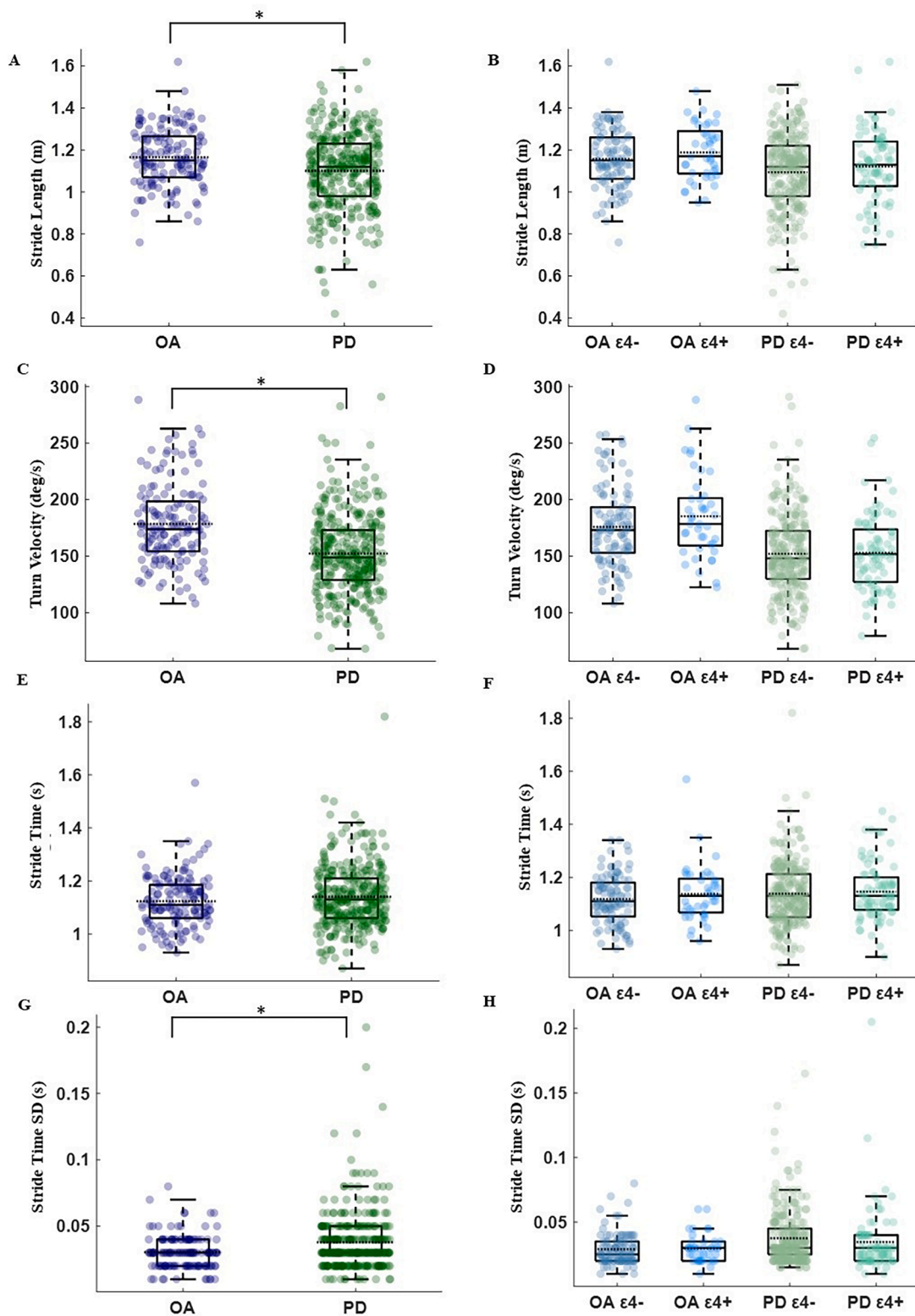


Fig. 1. Figure 1A (Top Panel) Gait characteristics in older adult (OA) and Parkinson's disease (PD) *APOE* $\epsilon 4$ carriers ($\epsilon 4+$) and *APOE* $\epsilon 4$ non-carriers ($\epsilon 4-$). A and B) stride length, C and D) turn velocity, E and F) stride time, and G and H) stride time variability. * denotes significance. Figure 1B (Bottom Panel) Balance characteristics in older adult (OA) and Parkinson's disease (PD) *APOE* $\epsilon 4$ carriers ($\epsilon 4+$) and *APOE* $\epsilon 4$ non-carriers ($\epsilon 4-$). A and B) sway jerk AP C and D) sway jerk ML, E and F) sway velocity AP, and G and H) sway frequency AP. * denotes significance.

assessment of gait under cognitively challenging conditions may provide a more sensitive measure of effects of *APOE* $\epsilon 4$. In comparison to gait, work assessing balance associations with *APOE* $\epsilon 4$ is very limited. One

previous study assessed objective balance measures in OA, but no differences were observed between carriers and non-carriers [13]. Therefore, our cross-sectional findings of single-task gait and balance mirror

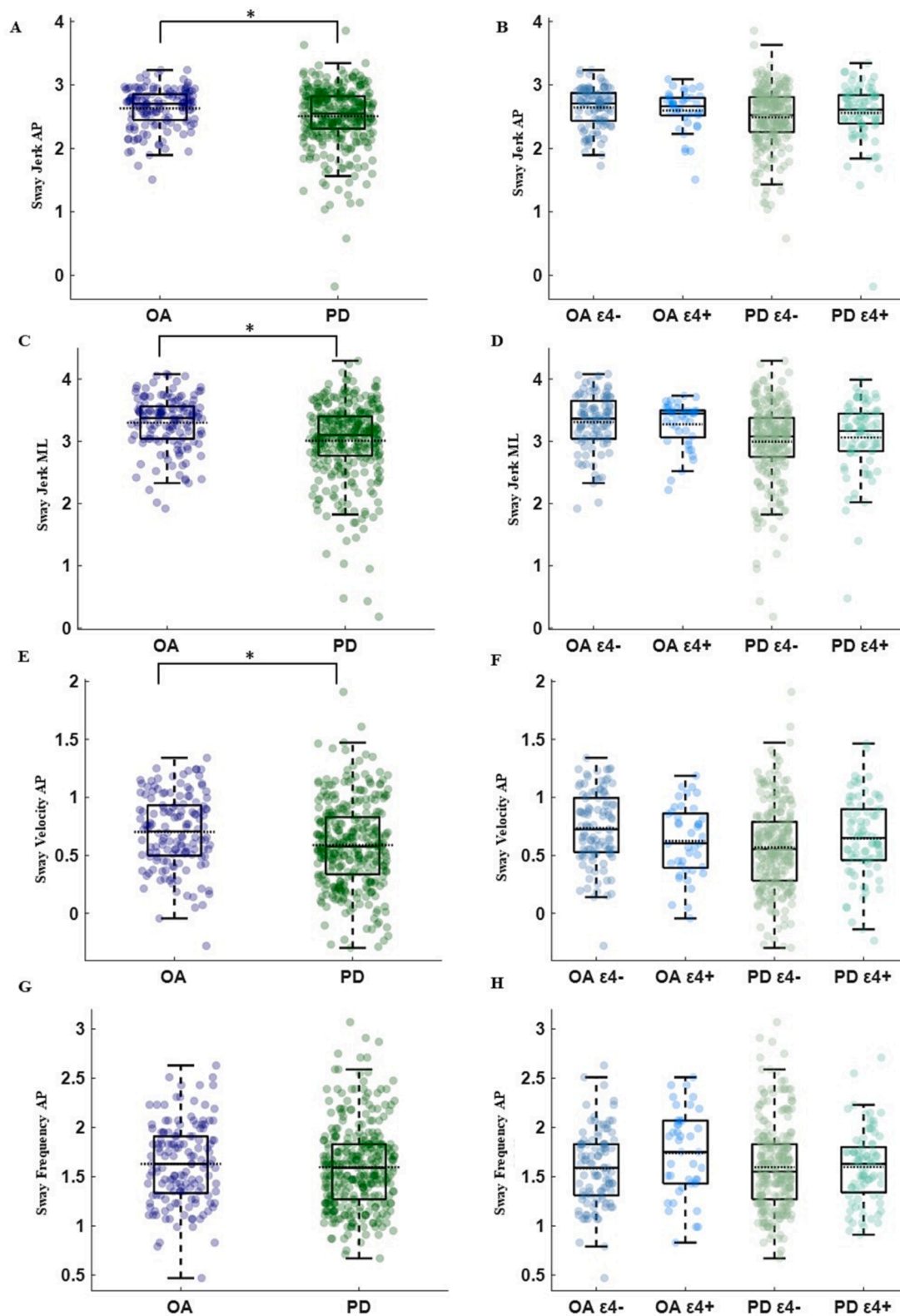


Fig. 1. (continued).

findings of those in OA and may demonstrate that *APOE* ε4 status is distinct from mobility deficits associated with both ageing and PD. Work needs to be done to assess gait under dual-task conditions to decipher whether assessing gait under more challenging conditions helps to differentiate between carriers and non-carriers of *APOE* ε4 in either OA or PD populations.

Assessment of comprehensive gait and balance deficits in PD *APOE* ε4 carriers as disease progresses is also a future area of interest, as gait speed in healthy OA was found to decline more rapidly in *APOE* ε4 carriers compared to non-carriers [15]. Although there is no work to date examining longitudinal changes in objective measures of gait and balance associated with *APOE* ε4, recent publications have used clinical

Table 3
Gait and balance characteristics for older adults and Parkinson's disease who are carriers and non-carriers of the APOE ε4 allele.

	OA APOE ε4		OA		OA APOE ε4		PD APOE ε4		PD APOE ε4		PD APOE ε4		Group*APOE ε4 [†]		Group*APOE ε4 [†]	
	Non-Carrier (N = 103)	ε4 Carrier (N = 41)	Group [†]		Adjusted Cognition ^ψ		Non-Carrier (N = 253)		ε4 Carrier (N = 81)	Group [†]		Adjusted Cognition ^ψ		ε4 [†]		Adjusted Cognition ^ψ
	Mean (SD)	Mean (SD)	F	p	F	p	Mean (SD)	Mean (SD)	F	p	F	p	F	p	F	p
Gait																
Gait Speed (m/s)	1.04 (0.15)	1.06 (0.16)	0.116	0.734	0.290	0.591	0.97 (0.20)	0.99 (0.17)	0.035	0.853	0.332	0.565	0.024	0.877	0.178	0.673
Stride Length (m)	1.16 (0.14)	1.19 (0.13)	1.62	0.205	1.93	0.168	1.09 (0.18)	1.12 (0.17)	0.388	0.534	1.32	0.252	0.204	0.651	0.529	0.467
Foot Strike Angle (deg)	22.94 (5.27)	24.12 (3.98)	1.46	0.229	1.65	0.201	18.87 (6.16)	19.68 (6.14)	0.248	0.619	0.837	0.361	0.322	0.571	0.619	0.432
Turn Velocity (deg/s)	175.87 (34.23)	185.30 (37.29)	1.99	0.160	2.00	0.160	152.13 (35.39)	152.92 (32.70)	0.040	0.842	0.000	0.988	1.61	0.205	2.00	0.158
Stride Time (s)	1.12 (0.09)	1.14 (0.11)	1.36	0.245	1.08	0.300	1.14 (0.12)	1.15 (0.11)	0.167	0.683	0.198	0.657	0.352	0.553	0.262	0.609
Stride Length SD (m)	0.048 (0.020)	0.048 (0.028)	0.001	0.975	0.028	0.866	0.058 (0.025)	0.053 (0.022)	1.99	0.159	2.22	0.138	0.582	0.446	0.436	0.509
Foot Strike Angle SD (deg)	2.177 (0.704)	2.232 (0.745)	0.455	0.501	0.160	0.689	2.568 (0.890)	2.440 (0.964)	1.26	0.262	1.49	0.224	0.880	0.349	0.553	0.457
Stride Time SD (s)	0.029 (0.012)	0.030 (0.011)	0.158	0.692	0.054	0.817	0.038 (0.021)	0.035 (0.0255)	1.15	0.284	1.81	0.180	0.660	0.417	0.392	0.532
Double Support Time (% GCT)	21.92 (3.59)	21.58 (3.34)	0.141	0.708	0.418	0.519	22.01 (4.01)	21.87 (3.51)	0.004	0.952	0.050	0.823	0.259	0.611	0.273	0.601
Sway Area [†] (m ² /s ⁵)	0.004 (0.004)	0.004 (0.004)	1.43	0.234	1.15	0.286	0.013 (0.037)	0.016 (0.092)	0.844	0.359	1.15	0.285	1.43	0.232	1.18	0.279
AP Jerk [†] (m ² /s ⁵)	0.003 (0.003)	0.004 (0.005)	1.23	0.270	1.67	0.199	0.007 (0.020)	0.022 (0.167)	0.440	0.507	0.627	0.429	0.956	0.329	0.909	0.341
ML Jerk [†] (m ² /s ⁵)	0.001 (0.002)	0.001 (0.001)	0.490	0.485	0.643	0.424	0.007 (0.049)	0.006 (0.037)	0.330	0.566	0.635	0.426	0.398	0.528	0.313	0.576
AP RMS [†] (m/s ²)	0.076 (0.037)	0.083 (0.037)	2.11	0.148	0.991	0.321	0.103 (0.070)	0.094 (0.091)	1.65	0.200	1.62	0.204	2.99	0.084	2.36	0.125
ML RMS [†] (m/s ²)	0.027 (0.018)	0.027 (0.015)	0.368	0.545	0.227	0.635	0.044 (0.041)	0.040 (0.044)	0.226	0.635	0.430	0.513	0.408	0.523	0.260	0.611
AP Velocity [†] (m/s ²)	0.243 (0.230)	0.304 (0.233)	3.89	0.050	1.58	0.212	0.375 (0.327)	0.308 (0.390)	2.01	0.157	1.81	0.180	5.38	0.021	4.33	0.038
ML Velocity [†] (m/s ²)	0.109 (0.102)	0.104 (0.083)	0.021	0.885	0.002	0.963	0.157 (0.151)	0.142 (0.123)	0.002	0.966	0.019	0.890	0.019	0.890	0.001	0.976
AP Frequency 95% (Hz)	1.584 (0.385)	1.740 (0.437)	4.82	0.030	6.09	0.015	1.595 (0.438)	1.597 (0.366)	0.182	0.670	0.075	0.784	2.24	0.135	2.37	0.125
ML Frequency 95% (Hz)	2.316 (0.518)	2.296 (0.520)	0.50	0.823	0.058	0.810	2.313 (0.542)	2.304 (0.509)	0.050	0.823	0.161	0.688	0.011	0.915	0.030	0.863

[†]Adjusted for age, gender, and testing site.

^ψ Adjusted for age, gender, testing site, and cognitive status.

[†] Variables natural log transformed for analysis.

SD = standard deviation, GCT = gait cycle time, AP = anterior-posterior, ML = medio-lateral, RMS = Root Mean Square.

motor assessments (MDS-UPDRS and H&Y) to determine motor progression of *APOE* ϵ 4 carriers in PD. Motor symptom trajectories did not differ for *APOE* ϵ 4 carriers compared to non-carriers in two studies [4,28], but one study identified that progression was quicker in carriers, but only in participants with high A β burden [29]. Interestingly, studies that did not identify a faster trajectory of motor progression did determine that cognitive function deteriorated at a quicker rate [4,28]. Given the association between motor function and cognition that is now well described in PD [11], with gait function predicting cognitive decline [30], it is of interest that motor and cognitive signs may not progress in parallel. These findings may indicate differing underlying pathology in *APOE* ϵ 4 carriers, in which cognitive domains known to contribute less to the control of gait and balance, such as memory, are impacted in *APOE* ϵ 4 carriers [30].

APOE ϵ 4 is strongly associated with A β deposition [3], with higher A β deposition seen in *APOE* ϵ 4 carriers compared to non-carriers [31]. In a cohort of newly diagnosed PD, low CSF levels of A β 42 and A β 40 predicted gait decline over three years suggesting a role for amyloid pathology in gait deficits [9]. This determines a role for A β pathology for gait in PD that is perhaps distinct from other pathology, such as α -synuclein. Furthermore, A β burden mediates the relationship between *APOE* ϵ 4 and freezing of gait (FOG), an episodic gait impairment [31,32] known to have higher incidence in PD *APOE* ϵ 4 carriers [31]. Future work should examine comprehensive characteristics of gait and balance longitudinally and associated with levels of A β burden to improve understanding of amyloid pathology underpinning gait and balance impairment. Furthermore, future work should study white matter hyperintensities in carriers and non-carriers to further inform the mechanisms proposed.

4.1. Clinical implications

A precision medicine approach to target heterogeneity in the progression of balance and gait impairment and the risk of falls is critical to improving rehabilitation. Unlike *GBA*- and *LRRK2*-related PD, those with the *APOE* ϵ 4 allele demonstrate the same gait and balance performance compared to those who are non-carriers. Therefore, knowledge of genetic status may impact how we rehabilitate our patients. However, progression of gait and balance impairment in *APOE* ϵ 4 carriers may be faster than noncarriers so longitudinal studies are needed to inform prognosis.

4.2. Strengths and limitations

This study provided a large cohort of *APOE* ϵ 4 carriers, both in OA and PD groups, with comprehensive measurements of gait and balance. However, there are several limitations that need to be addressed. First, we must acknowledge that there were a relatively smaller number of *APOE* ϵ 4 carriers compared to non-carriers in the OA group, although our samples represented larger numbers than normal incidence within the population. Second, we had a disproportionately large number of PD patients with *GBA* variants within our study due to the enrichment nature of study recruitment. Nevertheless, analysis was performed with removing this subgroup and had no impact on our findings. Third, this study assessed gait and balance in the 'on' medication state. Medication has been shown to improve many measures of gait, while the effects of balance are mixed. It is unclear if medication would differentially impact PD *APOE* ϵ 4 carriers and versus non-carriers, though it might be expected that carriers would have lesser improvements in gait due to involvement of non-DA pathways. Future work is needed to determine whether dopaminergic medication differentially impacts people with PD based on *APOE* ϵ 4 status. Finally, the current study is limited to cross-sectional assessment and therefore the progression of impairment is not currently understood and should be examined in future work.

4.3. Conclusions

This study is the first, to our knowledge, to assess differences in balance and gait in both OA and people with PD who are carriers and non-carriers of the *APOE* ϵ 4 allele. In this study, we identified no differences in gait or balance measures in either OA or PD who carried the *APOE* ϵ 4 allele compared to those who were non-carriers. Future work is needed to assess progression of gait and balance deficits in PD *APOE* ϵ 4 carriers to determine whether the trajectory of impairment is comparable to non-carriers.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: VEK has received grant support from the report's grants from NIH, Department of Veterans Affairs, and University of Washington and is an external advisor for projects by Sage Bionetworks. BC is supported by grants from the NIH. CPZ is supported by grants from the NIH, Department of Veterans Affairs, and the American Parkinson Disease Association. KP has received grants from the NIH, clinical trial funded by Sanofi and consulting for Allergan. KLE has received grants from the NIH. TJM has received grants from the NIH and Farmer Family Foundation. JFQ receives compensation for conducting clinical trials for Roche, Sanofi, Abbvie and member of DSMB vTv pharmaceuticals. FH has a significant financial interest in APDM, a division of Clario Int, a company that may have a commercial interest in the results of this research and technology. This potential institutional and individual conflict has been reviewed and managed by OHSU. RM, DNM, KR, KS, AH, KAC, SCH, IM, and JL have nothing to declare.

Acknowledgements

This work was supported by grants from the National Institutes of Health (NIH) (Pacific Udall Center; P50 NS062684) and the Department of Veterans Affairs (101 CX001702), and by infrastructure provided by the Veterans Affairs Northwest Parkinson's Disease Research, Education, and Clinical Center. This publication was made possible with support from the Oregon Clinical and Translational Research Institute (OCTRI), grant number UL1TR002369 from the National Center for Advancing Translational Sciences (NCATS), a component of the NIH, and NIH Roadmap for Medical Research.

Author contributions

RM- data acquisition, statistical data analysis, drafting of the paper.
 DNM- data acquisition, critical revision of the paper.
 KR- statistical data analysis, critical revision of the paper.
 VEK- data acquisition, critical revision of the paper.
 KS- data acquisition, critical revision of the paper.
 AH- data acquisition, critical revision of the paper.
 KAC- data acquisition, critical revision of the paper.
 SCH- data acquisition, critical revision of the paper.
 CPZ- study concept and design, data acquisition, critical revision of the paper.
 KP- study concept and design, data acquisition, critical revision of the paper.
 IM- study concept and design, data acquisition, critical revision of the paper.
 KLE- study concept and design, data acquisition, critical revision of the paper.
 JL- statistical data analysis, critical revision of the paper.
 BC- study concept and design, data acquisition, critical revision of the paper.
 TJM- study concept and design, data acquisition, critical revision of the paper.

JFQ- study concept and design, data acquisition, critical revision of the paper.

FH- study concept and design, data acquisition, drafting of the paper, critical revision of the paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.prdoa.2023.100201>.

References

- [1] C. Curtze, J.G. Nutt, P. Carlson-Kuhta, M. Mancini, F.B. Horak, Levodopa is a double-edged sword for balance and gait in people with Parkinson's disease, *Mov Disord* 30 (10) (2015) 1361–1370.
- [2] S.A. Schneider, B. Hizli, R.N. Alcalay, Emerging targeted therapeutics for genetic subtypes of Parkinsonism, *Neurotherapeutics* 17 (4) (2020) 1378–1392.
- [3] Y.u. Yamazaki, N.a. Zhao, T.R. Caulfield, C.-C. Liu, G. Bu, Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies, *Nat. Rev. Neurol.* 15 (9) (2019) 501–518.
- [4] S. Jo, S.-O. Kim, K.W. Park, S.H. Lee, Y.S. Hwang, S.J. Chung, The role of APOE in cognitive trajectories and motor decline in Parkinson's disease, *Sci. Rep.* 11 (1) (2021).
- [5] N. Pankratz, L. Byder, C. Halter, A. Rudolph, C.W. Shults, P.M. Conneally, T. Foroud, W.C. Nichols, Presence of an APOE4 allele results in significantly earlier onset of Parkinson's disease and a higher risk with dementia, *Mov. Disord.* 21 (1) (2006) 45–49.
- [6] I.F. Mata, J.B. Leverenz, D. Weintraub, J.Q. Trojanowski, H.I. Hurtig, V.M. Van Deerlin, B. Ritz, R. Rausch, S.L. Rhodes, S.A. Factor, C. Wood-Siverio, J.F. Quinn, K. A. Chung, A.L. Peterson, A.J. Espay, F.J. Revilla, J. Devoto, S.-C. Hu, B. A. Cholerton, J.Y. Wan, T.J. Montine, K.L. Edwards, C.P. Zabetian, APOE, MAPT, and SNCA genes and cognitive performance in Parkinson disease, *JAMA Neurol.* 71 (11) (2014) 1405.
- [7] C. Nombela, J.B. Rowe, S.E. Winder-Rhodes, A. Hampshire, A.M. Owen, D. P. Breen, G.W. Duncan, T.K. Khoo, A.J. Yarnall, M.J. Firbank, P.F. Chinnery, T. W. Robbins, J.T. O'Brien, D.J. Brooks, D.J. Burn, R.A. Barker, Genetic impact on cognition and brain function in newly diagnosed Parkinson's disease: ICICLE-PD study, *Brain* 137 (10) (2014) 2743–2758.
- [8] C.H. Williams-Gray, A. Goris, M. Saiki, T. Foltynie, D.A.S. Compston, S.J. Sawcer, R.A. Barker, Apolipoprotein E genotype as a risk factor for susceptibility to and dementia in Parkinson's disease, *J. Neurol.* 256 (3) (2009) 493–498.
- [9] L. Rochester, B. Galna, S. Lord, A.J. Yarnall, R. Morris, G. Duncan, T.K. Khoo, B. Mollenhauer, D.J. Burn, Decrease in A β 42 predicts dopa-resistant gait progression in early Parkinson disease, *Neurology* 88 (16) (2017) 1501–1511.
- [10] J.T. Boonstra, S. Michielse, Y. Temel, G. Hoogland, A. Jahanshahi, Neuroimaging detectable differences between Parkinson's disease motor subtypes: A systematic review, *Move. Disord. Clin. Pract.* 8 (2) (2021) 175–192.
- [11] R. Morris, S. Lord, J. Bunce, D. Burn, L. Rochester, Gait and cognition: Mapping the global and discrete relationships in ageing and neurodegenerative disease, *Neurosci. Biobehav. Rev.* 64 (2016) 326–345.
- [12] R.K. MacAulay, T. Allaire, R. Brouillette, H. Foil, A.J. Bruce-Keller, J.N. Keller, J. Vina, Apolipoprotein E genotype linked to spatial gait characteristics: predictors of cognitive dual task gait change, *PLoS One* 11 (8) (2016), e0156732.
- [13] J.R. Biggan, W.E. Taylor, K. Moss, L. Adumatiog, V. Shannon, R.J. Gatchel, C. T. Ray, Role of ApoE- ϵ 4 genotype in gait and balance in older adults: A pilot study, *J. Appl. Biobeh. Res.* 22 (2) (2017), e12061.
- [14] H.E. Whitson, G.G. Potter, J.A. Feld, B.L. Plassman, K. Reynolds, R. Sloane, K. A. Welsh-Bohmer, Dual-task gait and Alzheimer's disease genetic risk in cognitively normal adults: A pilot study, *J. Alzheimers Dis.* 64 (4) (2018) 1137–1148.
- [15] J. Verghese, R. Holtzer, C. Wang, M.J. Katz, N. Barzilai, R.B. Lipton, Role of APOE genotype in gait decline and disability in aging, *J. Gerontol.: Series A* 68 (11) (2013) 1395–1401.
- [16] R. Sakurai, M. Montero-Odasso, Apolipoprotein E4 allele and gait performance in mild cognitive impairment: results from the gait and brain study, *J. Gerontol.: Ser. A* 72 (12) (2017) 1676–1682.
- [17] B.A. Cholerton, C.P. Zabetian, J.F. Quinn, K.A. Chung, A.L. Peterson-Hiller, L. J. Revilla, J. Devoto, G.S. Watson, S.-C. Hu, K.L. Edwards, T.J. Montine, J. B. Leverenz, Pacific Northwest Udall Center of excellence clinical consortium: study design and baseline cohort characteristics, *J. Parkinsons Dis.* 3 (2) (2013) 205–214.
- [18] T.E. Goldberg, E.D. Huey, D.P. Devanand, Association of APOE e2 genotype with Alzheimer's and non-Alzheimer's neurodegenerative pathologies, *Nat. Commun.* 11 (1) (2020) 4727.
- [19] M.Y. Davis, C.O. Johnson, J.B. Leverenz, D. Weintraub, J.Q. Trojanowski, A. Chen-Plotkin, V.M. Van Deerlin, J.F. Quinn, K.A. Chung, A.L. Peterson-Hiller, L. S. Rosenthal, T.M. Dawson, M.S. Albert, J.G. Goldman, G.T. Stebbins, B. Bernard, Z.K. Wszolek, O.A. Ross, D.W. Dickson, D. Eidelberg, P.J. Mattis, M. Niethammer, D. Yearout, S.-C. Hu, B.A. Cholerton, M. Smith, I.F. Mata, T.J. Montine, K. L. Edwards, C.P. Zabetian, Association of GBA mutations and the E326K polymorphism with motor and cognitive progression in Parkinson disease, *JAMA Neurol.* 73 (10) (2016) 1217.
- [20] R. Morris, D.N. Martini, K. Ramsey, V.E. Kelly, K. Smulders, A. Hiller, K.A. Chung, S.-C. Hu, C.P. Zabetian, K.L. Poston, I.F. Mata, K.L. Edwards, J. Lapidus, B. Cholerton, T.J. Montine, J.F. Quinn, F. Horak, Cognition as a mediator for gait and balance impairments in GBA-related Parkinson's disease, *npj Parkinson's Dis.* 8 (1) (2022).
- [21] K.S. Hruska, M.E. LaMarca, C.R. Scott, E. Sidransky, Gaucher disease: mutation and polymorphism spectrum in the glucocerebrosidase gene (GBA), *Hum. Mutat.* 29 (5) (2008) 567–583.
- [22] I.F. Mata, J.B. Leverenz, D. Weintraub, J.Q. Trojanowski, A. Chen-Plotkin, V. M. Van Deerlin, B. Ritz, R. Rausch, S.A. Factor, C. Wood-Siverio, J.F. Quinn, K. A. Chung, A.L. Peterson-Hiller, J.G. Goldman, G.T. Stebbins, B. Bernard, A. J. Espay, F.J. Revilla, J. Devoto, L.S. Rosenthal, T.M. Dawson, M.S. Albert, D. Tsuang, H. Huston, D. Yearout, S.-C. Hu, B.A. Cholerton, T.J. Montine, K. L. Edwards, C.P. Zabetian, GBA Variants are associated with a distinct pattern of cognitive deficits in Parkinson's disease, *Mov. Disord.* 31 (1) (2016) 95–102.
- [23] R. Morris, et al., Cognitive associations with comprehensive gait and balance measures in Parkinson's disease, *Parkinsonism Relat. Disord.* (2019).
- [24] R. Morris, S. Stuart, G. McBarron, P.C. Fino, M. Mancini, C. Curtze, Validity of Mobility Lab (version 2) for gait assessment in young adults, older adults and Parkinson's disease, *Physiol. Meas.* 40 (9) (2019), 095003.
- [25] M. Mancini, P. Carlson-Kuhta, C. Zampieri, J.G. Nutt, L. Chiari, F.B. Horak, Postural sway as a marker of progression in Parkinson's disease: A pilot longitudinal study, *Gait Posture* 36 (3) (2012) 471–476.
- [26] S. Pang, J. Li, Y. Zhang, J. Chen, Meta-Analysis of the relationship between the APOE gene and the onset of Parkinson's disease dementia, *Parkinson's Dis.* 2018 (2018) 1–12.
- [27] J.L. Robinson, E.B. Lee, S.X. Xie, L. Rennert, E. Suh, C. Bredenberg, C. Caswell, V. M. Van Deerlin, N. Yan, A. Yousef, H.I. Hurtig, A. Siderowf, M. Grossman, C. T. McMillan, B. Miller, J.E. Duda, D.J. Irwin, D. Wolk, L. Elman, L. McCluskey, A. Chen-Plotkin, D. Weintraub, S.E. Arnold, J. Brettschneider, V.-Y. Lee, J. Q. Trojanowski, Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated, *Brain* 141 (7) (2018) 2181–2193.
- [28] R. Kim, S. Park, D. Yoo, J.-S. Jun, B. Jeon, Impact of the apolipoprotein E ϵ 4 allele on early Parkinson's disease progression, *Parkinsonism Relat. Disord.* 83 (2021) 66–70.
- [29] J.L. Pu, et al., Apolipoprotein E genotype contributes to motor progression in Parkinson's disease, *Mov Disord* (2021).
- [30] R. Morris, S. Lord, R.A. Lawson, S. Coleman, B. Galna, G.W. Duncan, T.K. Khoo, A. J. Yarnall, D.J. Burn, L. Rochester, Gait rather than cognition predicts decline in specific cognitive domains in early Parkinson's disease, *J. Gerontol.: Series A* 72 (12) (2017) 1656–1662.
- [31] R. Kim, J.H. Shin, S. Park, H.-J. Kim, B. Jeon, Apolipoprotein E ϵ 4 genotype and risk of freezing of gait in Parkinson's disease, *Parkinsonism Relat. Disord.* 81 (2020) 173–178.
- [32] J.M. Hatcher-Martin, J.L. McKay, A.F. Pybus, B. Sommerfeld, J.C. Howell, F. C. Goldstein, L. Wood, W.T. Hu, S.A. Factor, Cerebrospinal fluid biomarkers in Parkinson's disease with freezing of gait: an exploratory analysis, *npj Parkinson's Dis.* 7 (1) (2021).