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Apolipoprotein E Alleles and Motor Signs in Older Adults with Alzheimer's Dementia

Ioannis Liampas [1,*], Silvia Demiri [2], Vasileios Siokas [1], Antonia Tsika [1], Chrysa Marogianni [1], Polyxeni Stamati [1], Grigorios Nasios [3], Lambros Messinis [4], Constantine G. Lyketsos [5] and Efthimios Dardiotis [1,5]

[1] Department of Neurology, University Hospital of Larissa, School of Medicine, University of Thessaly, Larissa 41100, Greece

[2] School of Medicine, University of Patras, Patras 26504, Greece

[3] Department of Speech and Language Therapy, School of Health Sciences, University of Ioannina, Ioannina 45500, Greece

[4] Laboratory of Neuropsychology and Behavioural Neuroscience, School of Psychology, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece

[5] Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD 21205, USA

* Correspondence: iliampas@uth.gr

Abstract

We investigated associations between *apolipoprotein E* (*APOE)* alleles and motor manifestations in Alzheimer's dementia (AD) capitalizing on NACC data. The baseline evaluations of older adults (≥60years) with a diagnosis of AD were analysed. Those with a concomitant diagnosis Parkinson's disease or other parkinsonian syndrome, and those treated with anti-parkinsonian agents were excluded. Three *APOE* groups were formed: *APOE2* (*APOE2* carriers), *APOE3* (*APOE3*/*APOE3*) and *APOE4* (*APOE4*/*APOE4, APOE4*/*APOE3*). UPDRS III was used to assess the presence or absence of motor signs in 9 domains. Adjusted binary logistic models featuring three *APOE* groups as exposures and motor domains as outcomes were estimated. Of 4979 included individuals, 389 were in the *APOE2*, 1799 in the *APOE3* and 2791 in the *APOE4* groups. Compared to the *APOE2* group, individuals in the APOE4 group had 36% (18-50%) lower odds of having at least one motor sign; 47% (19-66%) lower odds of rigidity, 44% (23-60%) lower odds of bradykinesia, 44% (22-63%) lower odds of impaired chair rise and 44% (19-64%) lower odds of impaired posture-gait. Exploratory analyses using *APOE* genotypes suggested dose-response relationships for both *APOE2* and *APOE4*. In conclusion, *APOE2* confers a risk towards motor (mainly parkinsonian) signs in AD. *APOE4* may have a protective effect.

Keywords: tremor; rigidity; bradykinesia; posture; gait

1. Introduction

Primarily expressed in astrocytes, the *apolipoprotein E* (*APOE)* gene encodes a multifunctional protein, key component of lipoprotein particles, involved in multiple homeostatic processes of the central nervous system; lipid transport, glucose metabolism, synaptic plasticity, neuroinflammation and vascular integrity, to name a few [1–3]. *APOE* has three major allelic variants *APOE2, APOE3,* and *APOE4*, which differ by single amino acid substitutions at positions 112 and 158 [4]. Individuals inherit one copy of the gene from each parent, resulting in six possible genotypes, with *APOE3*/*APOE3* being the most common [5].

APOE was the first genetic locus associated with the risk of late-onset Alzheimer's disease dementia (AD) in 1993 [6]. Carriers of a single *APOE4* allele have a 2 to 3-fold increased risk for AD, while those with two copies have a 10 to 15-fold greater risk [4]. Furthermore, *APOE4* is related to an

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earlier age of AD onset [7,8]. On the other hand, *APOE2* is linked to a lower risk of incident AD and a later age of disease onset [9,10]. Of note, across the AD continuum, *APOE2* has been linked to less prominent AD-related pathological alterations, more severe non-AD neuropathology, and atypical, non-amnestic AD phenotypes, [11–14]. Recently, *APOE2* was associated with more severe pathology in primary tauopathies such as progressive supranuclear palsy and corticobasal degenerations, supporting an association between *APOE2* and non-AD pathologies [15,16].

APOE is also implicated in the pathogenesis of α-synucleinopathies [17]. *APOE4* carriage increases the risk of Lewy Body Dementia, both Dementia with Lewy bodies and Parkinson's Disease (PD) Dementia [17]. In contrast, PD research established more complex associations: while meta-analyses initially supported a risk-conferring effect of *APOE2* towards PD [18,19], more recent studies suggested more complex, ethnic (or genotypic) associations [20,21].

Parkinsonian signs are present in AD with increasing frequency as the disease progresses [22]. Bradykinesia, rigidity and postural/gait disturbances are most commonly observed [22–25]. However, the determinants of motor signs in AD remain largely unknown. We investigated associations between *APOE* genotype and motor manifestations in AD. Based on the initial reports of the risk-conferring properties of *APOE2* towards PD, as well as the neuropathologic and atypical phenotypic associations of *APOE2* across the AD continuum, we hypothesized that *APOE2* alleles will increase the odds of having motor sings in AD. We capitalized on data from the Uniform Data Set (UDS), a central repository of data, stewarded by the National Alzheimer's Coordinating Center (NACC) [27].

2. Results

3.1 Participant Characteristics and Missing Data

The starting database included 44,713 individuals with at least one UDS evaluation. Among them, 15,363 were diagnosed with dementia and 11,196 with AD. Motor symptoms were assessed using the UPDRS-III only in the first two version of the UDS; thus, 2,249 participants evaluated on the 3rd version were excluded. Data on *APOE* were available for 6,742 of the 8,947 participants with AD and UPDRS-III assessments. After exclusion of those with a diagnosis of PD or other parkinsonian syndrome, those on anti-parkinsonian medication, and those under the age of 60 years, 5,810 participants were eligible for the present study (Figure 1).

Among eligible participants, 831 were missing data on at least one of the covariates (age, sex, race, education, MMSE, CDR, GDS and/or NPS). Individuals without missing data (*N*=4,979) were more often Caucasian ($p< 0.001$) and male ($p= 0.001$) compared to those without missing data (*N*=831). Action-postural tremor was more common in the former group ($p= 0.049$), whereas the remaining of the motor symptoms were more prevalent in the latter ($p< 0.001$). Those with missing data were older ($p= 0.010$), less educated ($p< 0.001$), performed worse on cognitive testing (MMSE, $p< 0.001$), had greater depression scores (GDS, $p= 0.001$), higher neuropsychiatric burden (NPS, $p< 0.001$) and greater cognitive severity (CDR, $p< 0.001$). There was no difference in terms of *APOE* genotypic distribution ($p= 0.152$). Among eligible participants without covariate missing data , none had missing data on resting tremor and rigidity, 2 had missing data on hypophonia, masked facies, action-postural tremor and/or bradykinesia, 22 on impaired posture-gait, 33 on impaired chair rise and 131 on postural instability. Therefore, slightly different participant subsets were analysed per motor domain.

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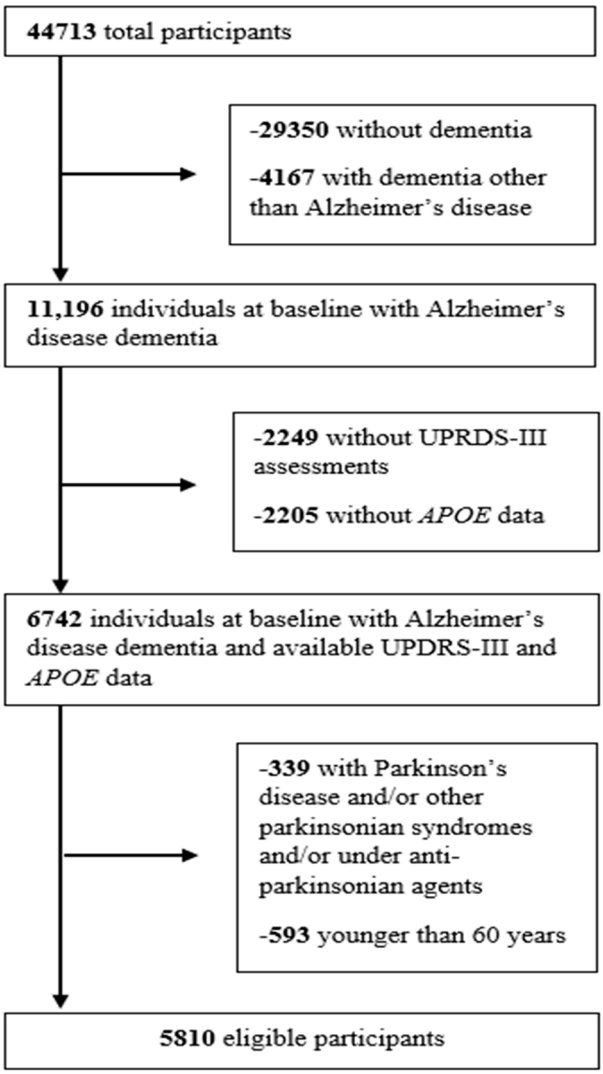

Figure 1. Participant flowchart.

Participant characteristics by *APOE* group are in Table 1. The *APOE4* group was younger and better educated compared to the other groups. The *APOE2* group had more participants of African American ancestry and fewer of Caucasian ancestry compared to the other groups. Sex distributions were similar among groups. Regarding clinical parameters, the *APOE4* group and had lower GDS scores compared to both other groups and performed worse on MMSE compared to the *APOE2* group. The *APOE2* group had lower global CDR scores than the others. NPS distributions were similar among groups. As for motor manifestations, a trend towards greater prevalence in the *APOE2* group and lower prevalence in the *APOE4* groups was documented (comparisons were significant in the context of rigidity, bradykinesia, impaired chair rise, impaired posture-gait and the global motor variable).

Table 1. Participant characteristics per *APOE* group.

Variable	*APOE2* (N=389)	*APOE3* (N=1799)	*APOE4* (N=2791)	p-value
Age (years)	77.6 ±8.1	77.9 ±8.3	75.3 ±7.4	P< 0.001
Sex (male/female)	176/213 (45.2/54.8)	850/949 (47.2/52.8)	1227/1564 (44.0/56..0)	p= 0.092
Education (years)	13.9 ±3.5	14.0 ±3.9	14.4 ±3.5	p= 0.001
Race (Caucasian / African American / Asian / other)	316/60/4/9 (81.2/15.4/1.0/2.3)	1519/181/29/70 (84.4/10.1/1.6/3.9)	2360/356/26/49 (84.6/12.8/0.9/1.8)	P< 0.001

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MMSE (30)	21.63 ±4.8	21.0 ±5.5	±20.8 ±5.4	p= 0.018
GDS (15)	2.8 ±2.8	2.6 ±2.6	2.4 ±2.5	p= 0.001
NPS (none/mild/ moderate or severe)	73/127/189 (18.8/32.6/48.6)	279/601/919 (15.5/33.4/51.1)	456/973/1362 (16.3/34.9/48.8)	p= 0.362
Global CDR (0.5/1.0/2.0/3.0)	151/196/41/1 (38.8/50.4/10.5/0.3)	605/868/279/47 (33.6/48.2/15.5/2.6)	959/1357/415/60 (34.4/48.6/14.9/2.1)	p= 0.012
Global motor variable (No / Yes)	266/123 (68.4/31.6)	1277/522 (71.0/29.0)	2157/634 (77.3/22.7)	P< 0.001
Hypophonia (No / Yes)	383/6 (98.5/1.5)	1770/27 (98.5/1.5)	2753/38 (98.6/1.4)	p= 0.907
Masked Facies (No / Yes)	379/10 (97.4/2.6)	1762/36 (98.0/2.0)	2738/52 (98.1/1.9)	p= 0.638
Resting tremor (No / Yes)	382/7 (98.2/1.8)	1768/31 (98.3/1.7)	2747/44 (98,4/1.6)	p= 0.902
Action – postural tremor (No / Yes)	362/27 (93.1/6.9)	1713/85 (95.3/4.7)	2671/119 (95.7/4.3)	p= 0.062
Rigidity (No / Yes)	360/29 (92.5/7.5)	1681/118 (93.4/6.6)	2655/126 (95.5/4.5)	p= 0.002
Bradykinesia (No / Yes)	337/52 (86.6/13.4)	1603/196 (89.1/10.9)	2546/243 (91.3/8.7)	p= 0.003
Impaired chair rise (No / Yes)	341/46 (88.1/11.9)	1606/181 (89.9/10.1)	2601/171 (93.8/6,2)	P< 0.001
Impaired posture – gait (No / Yes)	349/39 (89.9/10.1)	1635/157 (91.2/8.8)	2628/149 (94.6/5.4)	P< 0.001
Postural instability (No / Yes)	342/30 (91.9/8.1)	1613/129 (92.6/7.4)	2563/171 (93.7/6.3)	p= 0.199

Scale variables are presented in mean ± standard deviation; categorical variables are presented in absolute numbers (proportions); p-value corresponds to among group differences; N: number of individuals; *APOE*: *apolipoprotein*; MMSE: mini-mental state examination; GDS: geriatric depression scale; NPS: neuropsychiatric score; CDR: clinical dementia rating scale.

3.2. APOE Alleles and Motor Signs in Older Adults with AD

Crude binary logistic regression models revealed that compared to the *APOE2* group, the *APOE4* group exhibited lower odds having at least one motor sign [OR= 0.64, 95%CI= (0.50, 0.80)] (Table 2). Significant findings related to rigidity, bradykinesia, impaired chair rise and impaired posture gait. Adjusted models confirmed these findings (Table 2). In particular, individuals in the APOE4 group had 36% (18-50%) lower odds of having at least one motor sign, 47% (19-66%) lower odds of rigidity, 44% (23-60%) lower odds of bradykinesia, 44% (22-63%) lower odds of impaired chair rise and 44% (19-64%) lower odds of impaired posture-gait (although the latter failed to achieve the stricter measure of statistical significance). Intermediate, statistically insignificant differences were found between the *APOE2* and *APOE3* groups using the stricter-corrected significance threshold of α= 0.005.

Table 2. Associations between *APOE* alleles and motor manifestations.

Variable	*APOE4* versus *APOE2*	*APOE3* versus *APOE2*
	Crude	
Global motor variable (p< 0.001)	0.64 (0.50, 0.80), p< 0.001	0.88 (0.70, 1.12), p= 0.307
Hypophonia (p= 0.907)	0.88 (0.37, 2.10), p= 0.775	0.97 (0.40, 2.38), p= 0.953
Masked Facies (p= 0.640)	0.72 (0.36, 1.43), p= 0.347	0.77 (0.38, 1.57), p= 0.480
Resting tremor (p=0.902)	0.87 (0.39, 1.95), p= 0.743	0.95 (0.42, 2.19), p= 0.917
Action – postural tremor (p= 0.065)	0.60 (0.39, 0.92), p= 0.019	0.67 (0.43, 1.04), p= 0.074
Rigidity (p= 0.003)	0.59 (0.39, 0.89), p= 0.013	0.87 (0.57, 1.33), p= 0.522
Bradykinesia (p= 0.003)	0.62 (0.45, 0.85), p= 0.003	0.79 (0.57, 1.10), p= 0.164

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Impaired chair rise (p< 0.001)	0.49 (0.35, 0.69), p< 0.001	0.84 (0.59, 1.18), p= 0.306
Impaired posture – gait (p< 0.001)	0.51 (0.35, 0.73), p< 0.001	0.86 (0.59, 1.24), p= 0.421
Postural instability (p= 0.200)	0.76 (0.51, 1.14), p= 0.184	0.91 (0.60, 1.38), p= 0.662
	Adjusted	
Global motor variable (p= 0.001)	0.64 (0.50, 0.82), p< 0.001	0.75 (0.59, 0.97), p= 0.027
Hypophonia (p= 0.623)	0.64 (0.26, 1.56), p= 0.331	0.67 (0.27, 1.71), p= 0.404
Masked Facies (p= 0.283)	0.58 (0.29, 1.16), p= 0.127	0.58 (0.28, 1.17), p= 0.136
Resting tremor (p=0.903)	0.83 (0.37, 1.87), p= 0.652	0.85 (0.37, 1.96), p= 0.699
Action – postural tremor (p= 0.047)	0.58 (0.38, 0.91), p= 0.017	0.59 (0.38, 0.93), p= 0.024
Rigidity (p= 0.004)	0.53 (0.34, 0.81), p= 0.004	0.74 (0.48, 1.14), p= 0.176
Bradykinesia (p= 0.002)	0.56 (0.40, 0.77), p= 0.001	0.65 (0.46, 0.91), p= 0.013
Impaired chair rise (p= 0.003)	0.54 (0.37, 0.78), p= 0.001	0.69 (0.47, 0.99), p= 0.046
Impaired posture – gait (p= 0.008)	0.54 (0.36, 0.81), p= 0.003	0.67 (0.45, 0.99), p= 0.046
Postural instability (p= 0.237)	0.88 (0.57, 1.34), p= 0.545	0.73 (0.47, 1.13), p= 0.163

APOE: *apolipoprotein*; effect sizes and precision estimates represent odds ratios and 95% confidence intervals; between group differences were considered significant only if among group differences were significant at the stricter-corrected p-value of α= 0.005.

Figure 2 shows the prevalence of motor manifestations by *APOE* group. Except for hypophonia, masked facies and resting tremor, a clear trend towards more frequent motor manifestations among *APOE2* carriers while less frequent in *APOE4* carriers, suggesting a dose-response pattern for both alleles. Exploratory analyses captured this dose-response relationship with bradykinesia, rigidity, impaired posture-gait and impaired chair rise (Table 3). Specifically, the *APOE2*/*APOE2* genotype was more closely associated with these signs than *APOE3*/*APOE2*. The latter exhibited more prominent associations than *APOE4*/*APOE2*. Sequentially, *APOE3*/*APOE4* and *APOE4*/*APOE4* genotypes exhibited relatively (compared to *APOE3*/*APOE3*) protective properties in an *APOE4* dose-dependent fashion. Overall, *APOE2* seemed to enlarge and *APOE4* to moderate the risk of these motor signs. On the other hand, the aforementioned pattern was not apparent in the remaining motor signs (with the potential exception of hypophonia) (Figure 3).

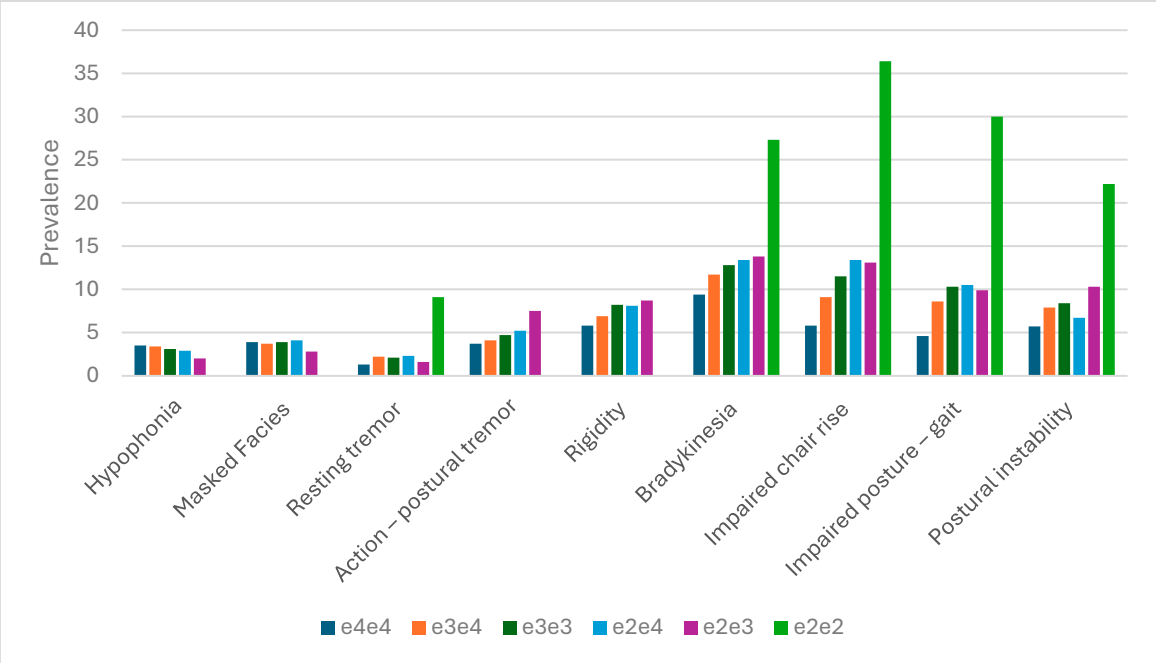

Figure 2. Prevalence of motor manifestations per *APOE* genotype.

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Table 3. Associations between *APOE* genotypes and motor manifestations. The *APOE3/APOE3* genotype was used as reference.

Variable	*APOE4/ APOE4*	*APOE3/ APOE4*	*APOE4/ APOE2*	*APOE3/ APOE2*	*APOE2/ APOE2*
Global motor variable (p= 0.003)	0.88 (p= 0.299)	0.84 (p= 0.029)	1.01 (p= 0.969)	1.57 (p= 0.004)	1.12 (p= 0.888)
Hypophonia (p= 0.906)	0.75 (p= 0.512)	1.01 (p= 0.982)	1.39 (p= 0.662)	1.62 (p= 0.397)	N/A
Masked Facies (p= 0.706)	0.92 (p= 0.813)	1.03 (p= 0.893)	1.89 (p= 0.240)	1.74 (p= 0.225)	N/A
Resting tremor (p=0.933)	0.69 (p= 0.393)	1.05 (p= 0.833)	1.34 (p= 0.637)	1.14 (p= 0.807)	N/A
Action – postural tremor (p= 0.206)	0.98 (p= 0.924)	0.99 (p= 0.943)	1.54 (p= 0.236)	1.88 (p= 0.021)	N/A
Rigidity (p= 0.013)	0.62 (p= 0.041)	0.74 (p= 0.034)	1.00 (p= 0.999)	1.66 (p= 0.045)	N/A
Bradykinesia (p= 0.006)	0.74 (p= 0.094)	0.88 (p= 0.259)	1.21 (p= 0.505)	1.67 (p= 0.015)	4.12 (p= 0.062)
Impaired chair rise (p= 0.029)	0.89 (p= 0.571)	0.77 (p= 0.037)	1.28 (p= 0.409)	1.55 (p= 0.058)	2.02 (p= 0.455)
Impaired posture – gait (p= 0.014)	0.64 (p= 0.082)	0.85 (p= 0.204)	1.15 (p= 0.677)	1.59 (p= 0.058)	6.40 (p= 0.039)
Postural instability (p= 0.349)	1.43 (p= 0.102)	1.15 (p= 0.293)	0.95 (p= 0.903)	1.62 (p= 0.063)	1.31 (p= 0.037)

APOE: *apolipoprotein*; effect sizes represent odds ratios; N/A: non-applicable due to lack of 'events'.

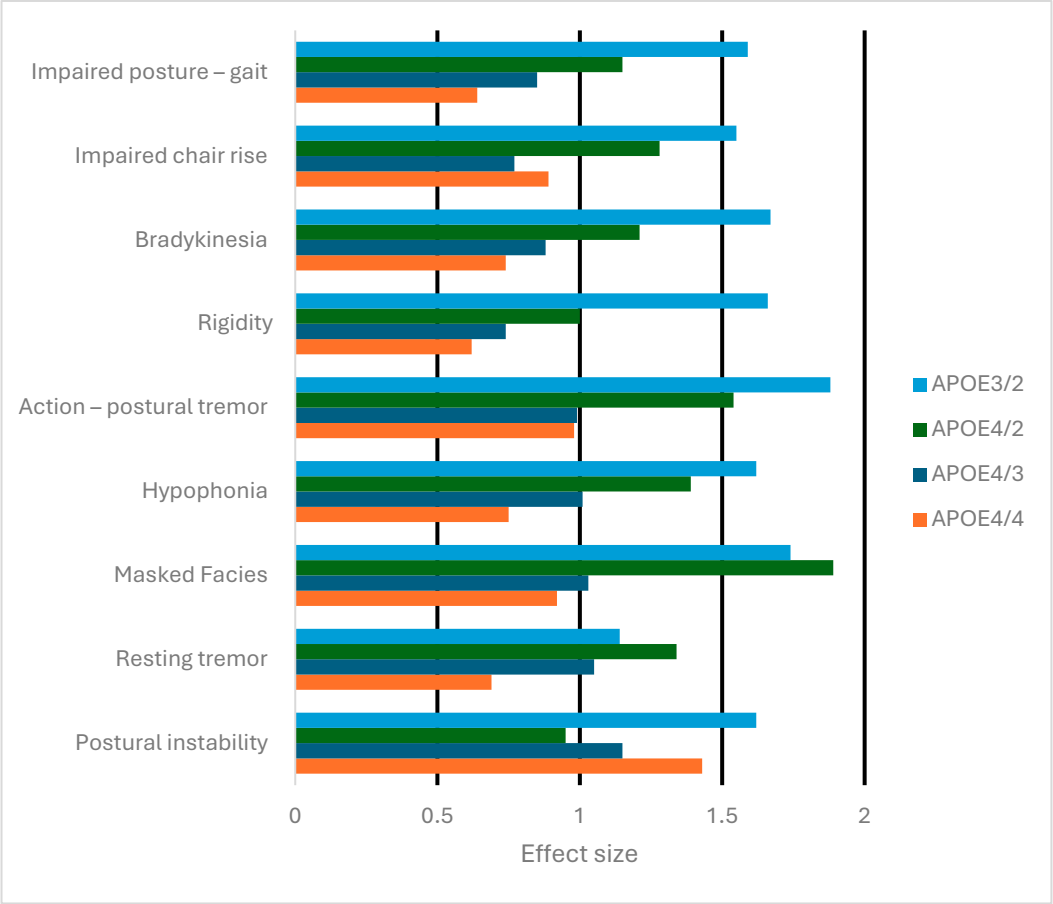

Figure 3. Dose-response trends in the associations between *APOE* genotypes and motor manifestations.

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3. Discussion

Compared to the *APOE4* allele, the *APOE2* allele confers a greater risk for motor signs in older adults with AD. These findings were most evident for bradykinesia, rigidity, impaired posture-gait and impaired chair rise. Intermediate, though statistically insignificant associations were found for the comparison of *APOE2* versus *APOE3*. The consistency (effect sizes and directions) and the p-values of theses associations ($p< 0.05$ for global motor variable, bradykinesia, impaired posture-gait, impaired chair rise) were indicative of a non-trivial differences between *APOE2* and *APOE3* (smaller than the difference between *APOE2* and *APOE4*). Exploratory analyses of *APOE* genotypes suggested a dose-response for both *APOE2* (risk-conferring properties) and *APOE4* (protective properties) with respect to motor signs.

While the risk-conferring effect of *APOE4* carriage towards major neurocognitive disorders such as AD, Dementia with Lewy Bodies and Parkinson's Disease Dementia, is well-established [17], the exact role of *APOE2* carriage in neurodegeneration is less clear. An overall protective effect has been reported for *APOE2* against the several dementias [9,10,28]. On the other hand, a risk-conferring effect for *APOE2* to PD has been reported [18,19]. Our findings concur that motor signs, especially parkinsonian manifestations (bradykinesia, rigidity, impaired posture-gait) in AD may be driven by *APOE2*. However, the pathophysiologic mechanisms behind this relationship remain unclear.

APOE2 may protect against β-amyloid accumulation, the neuropathological hallmark of AD [29]. It is associated with reduced global tau deposition in the AD continuum especially in the medial temporal regions, the earliest regions to display AD-related neurodegenerative alterations [30,31]. On the other hand, *APOE2* has been associated with primary tauopathies (e.g., progressive supranuclear palsy, argyrophilic grain disease) and more pronounced tau depositions in these entities [11,16,32]. Collectively, these findings suggest that APOE2 mitigates secondary tau deposition (as in AD) but drives primary tau pathology [15]. Hence, the relationship between *APOE2* and motor signs in AD is probably independent of its cognitive effects and may be related to the different neurodegeneration pattern that accompanies this allele. Less prominent β-amyloid pathological changes, less pronounced tau deposition in the entorhinal cortex and greater primary tau pathology, may explain the increased prevalence of motor signs associated with *APOE2*.

This study has several strengths including a large sample of genotyped older individuals with AD. The extensive characterization in the UDS allowed us to account for many important confounders: demographics, cognitive performance, depression scores, neuropsychiatric burden, AD stage [33]. Nevertheless, the analysis has several weaknesses as well, including being cross-sectional. Further, in most cases, the diagnosis of AD and other dementias was based on clinical criteria; biomarkers were not uniformly available. Therefore, there may have been misclassification of other neurodegenerative conditions as AD. As well, although several important covariates were considered, our findings may have been driven by residual confounding or non-trivial proportion of missing data. Next, although UPDRS-III is widely used in both clinical and research settings, variability can be expected across different examiners in quantifying motor signs. Finally, the count of some motor signs (hypophonia, resting tremor, masked facies) was very small, leading to lack of power in analyses involving these signs.

4. Materials and Methods

We analysed cross-sectional UDS data for associations between *APOE* alleles and motor signs in older adults with AD. The UDS assembles standardized, prospectively collected, multidisciplinary data from multiple National Institute on Aging / National Institutes of Health (NIA/NIH) - funded Alzheimer's Disease Centers (ADCs) across the United States [34]. The UDS is freely available to research scientists upon request (https://naccdata.org/). All study procedures were approved by Institutional Review Boards overseeing each ADC prior to the initiation of the study. All participants granted informed consent prior to participation. The rationale and the key methodological features of the UDS have been detailed elsewhere [35–37]. Briefly, each participating ADC enrols volunteers

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ranging from normal cognition to dementia. Participants may actively pursue professional consultation, may be referred to an ADC by other clinicians or family members, may be actively recruited, etc. Trained physicians and clinic personnel evaluate participants using a uniform, standardized protocol, on an approximately yearly basis. Although the focus of the UDS is AD, data are also collected on other neurocognitive and neuropsychiatric disorders.

2.1 Eligibility Criteria and Diagnostic Procedure

The present study was based on cross-sectional NACC data from the inception of the UDS (September 2005) to the December 2022 data freeze. Data from a total of 46 ADCs were involved. We focused on baseline evaluations of older adults, greater than 60 years old, with a diagnosis of AD but without a concomitant diagnosis of PD or a parkinsonian syndrome. Participants being treated with anti-parkinsonian medications were excluded. Depending on the specific protocol of each ADC, cognitive diagnoses were established by either an interdisciplinary consensus team (in most cases) or a single clinician (who examined the participant). Diagnoses were based on extensive standardized evaluations including personal and family medical history, clinical examinations, neuropsychological and neuropsychiatric assessments, psychosocial functioning evaluations, and so on. Dementia was diagnosed using standard clinical criteria [38–41]. Imaging and/or cerebrospinal fluid biomarkers were only available in a minority of participants [42,43].

2.2 Measurement of Motor Signs Based on the UPDRS-III

The Unified Parkinson's disease rating scale part III (UPDRS-III), which was administrated in the first two versions of the UDS, comprises 27 subitems. We grouped these into 9 domains as follows [44]: (1) hypophonia (single item); (2) masked facies (single item); (3) resting tremor (combined five items regarding tremor at rest in the face/lips/chin and four extremities); (4) action/postural tremor (combined two items regarding tremor at rest in the hands); (5) rigidity (combined five items regarding rigidity in the neck and four extremities); (6) bradykinesia (combined nine items: bilateral finger tapping, hand movements, rapid alternating movements of the hands, leg agility, and body bradykinesia); (7) impaired chair rise (single item); (8) impaired posture/gait (combined two items: posture and gait); and (9) postural instability (single item).

Each motor subitem was graded as absent (score <2) or present (score ≥2). The rationale for this cutoff is as follows: (1) this severity is more likely to be noted by the average clinician [45]; and (2) a score of 1 is suggestive of a very mild motor change that could be observed with normal aging [46]. Then, we created nine dichotomous variables (motor domains), such that participants were said to have an abnormal motor sign if they scored ≥2 in at least one of the subitems of the respective motor domain [47]. A global dichotomous variable was also created (presence of at least one motor sign), according to which participants were divided into those with (if they scored ≥2 in at least one motor domain) and those without (if they scored <2 in all motor domains) motor manifestations.

2.3 Apolipoprotein E Genotyping

APOE haplotypes for NACC were determined from the single-nucleotide variants *rs7412* (*APOE2*) and *rs42935848* (*APOE4*). We clustered participants into three groups, based on *APOE* genotypes: *APOE2* (*APOE2*/*APOE3, APOE2*/*APOE4, or APOE2*/*APOE2*), APOE*3* (*APOE3*/*APOE3*) or *APOE4* (*APOE3*/*APOE4 or APOE4*/*APOE4*).

2.4 Covariates Considered

Participant age at visit (years), education (years of formal schooling), Mini-Mental State Examination score (MMSE – cognitive performance) and Geriatric Depression Scale (GDS) scores were treated as scale variables. Sex (male/female), race (Caucasian, African American, Asian, other), global CDR (0.5, 1.0, 2.0, 3.0 – cognitive symptom severity) and neuropsychiatric symptom severity (NPS) – no, mild, moderate-severe NPS – were treated as categorical variables.

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NPS severity was assessed using data from the Neuropsychiatric Inventory Questionnaire (NPI-Q) (Cummings et al., 1994). NRI-Q evaluates 12 domains [delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, night-time behaviours, and appetite/eating] according to a 4-point severity scale: no, mild (noticeable, but not a significant change); moderate (significant, but not a dramatic change); or severe (very marked or prominent; a dramatic change). For each NPI-Q domain, participants were grouped into three categories: 0: absent; 1: mild; 2: moderate and severe symptomatology (due to the small prevalence of moderate and severe symptoms) [49]. Sequentially, the composite NPS was calculated as follows: 0: no symptoms; 1: at least one mild symptom with no moderate and/or severe symptoms, 2: at least one moderate and/or severe symptom.

2.5 Statistical Analysis

Differences between the three *APOE* groups were analysed using (1) analysis of variance with Bonferroni correction (scale variables) and (2) Pearson's chi-squared tests (categorical variables). Associations between the three *APOE* groups and motor signs were estimated using separate (for each motor domain) binary logistic regression models. Both crude and adjusted models were tested. Adjusted models featured the above set of covariates. A sequential exploratory analysis featuring the six individual *APOE* genotypes was performed, to assess for a dose-response (increased magnitude of effect sizes with homozygosity compared to heterozygosity). The exploratory analysis was identical to the main analysis (adjusted for the same covariates) except for the *APOE* variable, which featured the six *APOE* genotypes instead of the three *APOE* groups.

The analyses were performed using the IBM SPSS Statistics Software Version 27 (Chicago, IL, USA). The conventional threshold of α= 0.05 was implemented to assess for statistical significance in comparisons. The stricter α= 0.005 cut-point, corrected for multiple (N=10) comparisons, was used in the main analysis. Effect sizes (odds ratios, ORs) and precision estimates (95% confidence intervals, 95%CIs) are provided.

5. Conclusions

Compared to *APOE4*, *APOE2* confers an increased risk towards motor signs, including bradykinesia, rigidity, impaired posture-gait and impaired chair rise, in older adults with AD. *APOE3* may confer an intermediate risk. A dose-response relationship between *APOE2* vs. *APOE4* genotype with these motor signs may exist. These findings may have clinical implications for phenotypic subgroup definition and precision medicine. To explain these associations, future research applying more sophisticated imaging or post-mortem investigations should emphasize pathologic changes in older APOE2 carriers with AD.

Author Contributions: IL: conceptualization, design of the study, data curation, formal analysis, interpretation of data, original draft preparation, and review & editing of manuscript; SD: data curation, validation, original draft preparation, and review & editing of manuscript; VS, AT, CM,PS, GN & LM: validation, interpretation of data, and review & editing of manuscript; CGL & ED: conceptualization, design of the study, supervision, review & editing.

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Institutional Review Board & Informed Consent Statements: Not applicable: This cross-sectional analysis capitalised on data from the ongoing Uniform Data Set (UDS). UDS is a central repository of longitudinally collected data in National Institute on Aging—funded Alzheimer's Disease Research Centers (ADRCs) across the United States. UDS is stewarded by the National Alzheimer's Coordinating Center (NACC). Participants are enrolled according to each ADRC's discrete protocol. Written informed consent is obtained prior to participation. All procedures are overseen by Institutional Review Boards at each ADRC and performed in accordance with the ethical standards laid down in the declaration of Helsinki and its later amendments.

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Data Availability Statement: For further information on access to the NACC database, please contact NACC (contact details can be found at https://naccdata.org/).

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Abbreviations

The following abbreviations are used in this manuscript:

APOE	apolipoprotein E
AD	Alzheimer's Disease dementia
PD	Parkinson's Disease
UDS	Uniform Data Set
NACC	National Alzheimer's Coordinating Center
NIA/NIH	National Institute on Aging / National Institutes of Health
ADCs	Alzheimer's Disease Centers
UPDRS-III	Unified Parkinson's Disease Rating Scale part III
MMSE	Mini-Mental State Examination
GDS	Geriatric Depression Scale
CDR	Clinical Dementia Rating
NPS	Neuropsychiatric Symptom Severity
NPI-Q	Neuropsychiatric Inventory Questionnaire
ORs	Odds Ratios
95%CIs	95% Confidence Intervals

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