Published in final edited form as:

J Alzheimers Dis. 2017 ; 55(4): 1519–1528. doi:10.3233/JAD-160780.

Risk Factors and Pathological Substrates Associated with Agitation/Aggression in Alzheimer's Disease: A Preliminary Study using NACC Data

Simrin Sennik[a], **Tom A. Schweizer**[a,b,c,d,e], **Corinne E. Fischer**[a,f], and **David G. Munoz**[a,g,h,*]

[a]Keenan Biomedical Research Centre, the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada

[b]Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada

[c]Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, ON, Canada

[d]Department of Surgery, Division of Neurosurgery, Faculty of Medicine, University of Toronto, ON, Canada

[e]Division of Neurosurgery, St. Michael's Hospital, Toronto, ON, Canada

[f]Department of Psychiatry, Faculty of Medicine, University of Toronto, ON, Canada

[g]Department of Laboratory Medicine and Pathobiology, University of Toronto, ON, Canada

[h]Department of Laboratory Medicine, St. Michael's Hospital, Toronto, ON, Canada

Abstract

Background—Neuropsychiatric symptoms are common manifestations of Alzheimer's disease (AD). A number of studies have targeted psychosis, i.e., hallucinations and delusions in AD, but few have assessed agitation/aggression in AD.

Objective—To investigate the risk factors and pathological substrates associated with presence [A(+)] and absence [A(−)] of agitation/aggression (A) in autopsy-confirmed AD.

Methods—Data was collected from the UDS data as of 2015 on the NACC database. Patients were stratified as intermediate (IAD) or high (HAD) pathological load of AD. Clinical diagnoses were not considered; additional pathological diagnoses were treated as variables. Analysis of data did not include a control group or corrections for multiple comparisons.

Results—1,716 patients met the eligibility criteria; 34.6% of the IAD and 49.6% of the HAD patients were A(+), indicating an association with severity of pathology ($p = 0.001$). Risk factors for A(+) included: age at initial visit, age at death, years of education, smoking (in females), recent cardiac events (in males), and clinical history of traumatic brain injury (TBI) (in males). A history of hypertension was not related to A(+). In terms of comorbidity, clinical diagnosis of Lewy body dementia syndrome was associated with A(+)but the association was not confirmed when

*Correspondence to: Dr. David G. Munoz, Department of Laboratory Medicine, Room 2-097 CC Wing, St. Michael's Hospital, 30 Bond Street. Toronto, M5B 1W8. ON, Canada. Tel.: +1 416 864 5858; Fax: +1 416 864 5648; MunozD@smh.ca.

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/16-0780r2).

pathological diagnosis based on demonstration of Lewy bodies was used as the criterion. The additional presence of phosphorylated TDP-43, but not tau pathologies, was associated with A(+)HAD. Vascular lesions, including lacunes, large arterial infarcts, and severity of atherosclerosis were negatively associated with A(+). Associated symptoms included delusions, hallucinations, and depression, but not irritability, aberrant motor behavior, sleep and night time behavioral changes, or changes in appetite and eating habits.

Conclusions—Smoking, TBI, and phosphorylated TDP-43 are associated with A(+)AD in specific groups, respectively. A(+) is directly associated with AD pathology load and inversely with vascular lesions.

Keywords

Alzheimer's disease; agitation; aggression; neuropathology; (p)-TDP-43; traumatic brain injury; vascular lesions; vascular risk factors

INTRODUCTION

Neuropsychiatric symptoms, including depression, hallucinations, delusions, anxiety, apathy, and agitation/aggression are common manifestations of Alzheimer's disease (AD). A number of studies have targeted psychosis, i.e., hallucinations and delusions, in AD. The few studies on agitation/aggression in AD have assessed its associations in terms of cognitive function and neurotransmitter receptor gene polymorphisms in probable AD (without autopsy diagnosis), and limited neuropathology on small sample sizes in definite AD (with autopsy diagnosis) [2, 3]. This study will focus on the relationship between presence [A(+)] and absence [A(−)] of agitation/aggression (A) in pathologically confirmed AD, including both intermediate (IAD) and high (HAD) pathology load groups in a large sample. The subject was considered (A+) if scored as positive in AGIT in any visit. The variables assessed include risk factors, lesions, co-morbidities, and symptom associations.

MATERIALS AND METHODS

Data source and subject criteria

The National Alzheimer's Coordinating Center's (NACC) Neuropathology (NP) and Uniform Data Sets (UDS) were used. Inclusion criteria for this study consisted of autopsy with evaluation of pathology by NIA-Reagan (NIA) criteria, aggression/agitation assessment via Neuropsychiatric Inventory, and Quick version (NPI-Q). The NACC population consisted of 32,064 subjects collected and compiled from 34 past and present AD centers between 2005 and 2015.Of these patients, 1,961 had autopsies with NIA evaluation. Braak & Braak staging for neurofibrillary tangles (Stages I-VI) and CERAD scores in the NP data set were combined to classify these patients by severity of pathology load. Subjects with intermediate likelihood of AD (N = 285), corresponding to a BRAAK stage of III or IV and CERAD score of 2, were classified for the purposes of our study as intermediate load Alzheimer's disease (IAD). Likewise, subjects with high likelihood of AD (N = 1,514), corresponding to a Braak stage of V or VI; CERAD score of 3, were classified as high load Alzheimer's disease (HAD). Agitation/aggression was identified by the NPI-Q in terms of presence (AGIT: Is the patient stubborn and resistive to help from others?) during the month

prior to the visit [1]. Out of the IAD and HAD groups, 257 IAD and 1,459 HAD patients were assessed for agitation/aggression. Therefore, 1,716 patients met the inclusion criteria. Clinical diagnoses were not considered as selection criteria. The presence of other pathologies was not an exclusion criterion. 49.6% (724/1459) of HAD patients had A(+) and 34.6% (89/257) of IAD patients had A(+) ($p = 0.0001$).

TDP-43 staining was not performed until the most recent version of the NP form implemented in January 2014. Assessment of vascular pathology was derived from the NACC data set. The NP forms were reported by AD centers and were directly sent to NACC [1]. Data for *APOE* genotype was reported by individual autopsy centers, as well as confirmed by Alzheimer's Disease Genetic Consortium (ADGC) reports. When assessing the *APOE* genotype, the samples were stratified based on number of *APOE* ε4 alleles: none, 1 copy, and 2 copies. Patients received standardized clinical evaluations and approximate annual follow-ups for the duration of their participation in the NACC study.

Statistical analysis

All the statistical analyses were done using SPSS Statistics 23.0 statistical software. The category of agitation/aggression was analyzed against specific variables. The χ^2 test was used for categorical data. The independent samples *t*-test was used for continuous data with normal distribution. Mann-Whitney test was used for continuous data if Kolmogorov-Smirnov test of normality was statistically significant. Ordinal regression was used for ordinal data. Statistical analysis was not corrected for multiple testing. Statistical significance was assessed using $\alpha = 0.05$. Data was stratified by both severity of pathology and gender.

The average time from when the patients were last clinically assessed to autopsy was non-significantly different between A(−) and A(+) subjects: (1.35±1.16SD years for A(+)IAD, 1.27±1.23SD years for A(−)IAD, 1.95±1.77SD years for A(+)HAD, and 1.97±1.89SD years for A(−)HAD).

RESULTS

Risk factors

A(+) was more common in males than females with IAD; no significance was reached in the HAD group. A(+) patients in both AD groups were younger at baseline during the NACC study and died at a younger age; this was significant in females. Years of education was positively associated with A(+)HAD. There were no associations with APOE genotypes either for one or two ε4 alleles. There were no correlations with family history of AD, or race (Table 2).

A(+)IAD patients smoked more packs per day, had an increased number of packs per year, and had more frequently smoked greater than 100 cigarettes in total than A(−)IAD. When stratified by gender, these correlations reached significance in females only. Alcohol abuse did not associate with A(+)AD (Table 2).

History of hypertension was not associated with A(+). Recent transient ischemic attack (TIA; within the last 6 months pre-autopsy) was associated with A(+)IAD, as did recent heart attack or cardiac arrest, both significant in males only (Table 2).

Clinical diagnosis of traumatic brain injury (TBI) at any point in life was more prevalent in A(+)HAD; reaching significance in males only (Table 2). There were no correlations with other vascular risk factors such as atrial fibrillation or type II diabetes mellitus.

Lesions

The presence of large arterial infarcts, and infarcts and lacunes detected at autopsy were negatively associated with A(+)IAD. Increased severity of atherosclerosis of the circle of Willis also inversely associated with A(+)HAD. There were no other significant vascular associations (Table 3).

Comorbidities

Clinical diagnosis of Lewy Body Dementia Syndrome (LBDS) was significantly more common in A(+)IAD females, and all A(+)HAD patients. However, this association did not hold when pathological confirmation of alpha-synuclein deposits was used. The clinical diagnosis of FTD was associated with A(+)HAD males. A(+)HAD patients more commonly had phosphorylated TDP-43 deposits and this was significant in males. On the other hand, the presence of non-AD tauopathy was not associated with aggression. Clinical and pathological diagnoses of progressive supranuclear palsy, Parkinson's disease, or multiple system atrophy did not associate with A(+) (Table 4).

Symptom associations

Clinical dementia rating (CDR) was significantly greater in A(+)IAD males, but not females and A(+)HAD males and females (Table 5). From a cognitive and functional point of view [Mini-Mental State Examination (MMSE) and Functional Activities Questionnaire (FAQ)], A(+) patients scored worse than A(−) patients. The presence of delusions was associated with A(+) IAD and A(+) HAD in both males and females. The presence of hallucinations was associated with A(+) IAD females and A(+) HAD males and females. A clinical diagnosis of depression was associated with A(+) IAD males and A(+)HAD males and females (Table 5). There were no associations with other behavioral symptoms such as irritability, aberrant motor behavior, sleep and night time behavioral changes, or changes in appetite and eating habits.

DISCUSSION

To our knowledge, this study is the first to analyze the correlates of A(+) in pathologically-confirmed AD in a large number of patients, with stratification by gender. We found that there is a 47.38% prevalence of A(+) in AD. Some of our findings were consistent with previous studies. CDR, MMSE, and FAQ results were as expected; A(+) patients scored higher on CDR, less on cognitive assessment (MMSE), and were more dependent (scored higher on FAQ) than A(−) patients. The presence of delusions and hallucinations was associated with A(+), in agreement with previous reports [4]. A study by Lopez et al. found

that a greater severity of dementia was associated with increased presence of neuropsychiatric symptoms, in clinically diagnosed AD, and there was a higher occurrence of A(+) in male AD patients (n = 1,155 based on NINCDS-ADRDA criteria) [8]. Our findings that A(+) is more common in HAD than IAD as determined by lesion load are consistent with Lopez et al.'s results in probable AD.

Some of our findings are in contrast to previous reports: we found that both A(+)AD groups were younger and died at a younger age than A(−) patients; this was significant in females only, contrary to a report on a small number of subjects (N = 75) of no association with age [4]. A study by Tekin et al. reported a non-significant negative association with education years and severity of agitation (N = 31, definite AD) [3], whereas we found an unexpected significant positive association between years of education and A(+)HAD.

Some of our findings in this study are novel. A(+)IAD is associated with smoking, significantly so in females only. This association in females may be due to biological effects of tobacco, but also could be related to personality and societal factors, as these women would have started smoking in approximately the 1930s when it may have been regarded as a defiant behavior. Alcohol abuse, defined in NACC as "clinically significant impairment occurring over a 12-month period manifested in one of the following areas: work, driving, legal, or social" [1], surprisingly did not associate with A(+), possibly because it was very uncommon in this population. Furthermore, despite hypertension, hyperlipidemia, and hyper-homocysteinemia having been found as important risk factors for the clinical diagnosis of AD, vascular risk factors other than smoking do not associate with A(+)AD [9]. Additionally, chronic vascular lesions identified at autopsy were negatively associated with A(+)AD. However A(+) in AD significantly associates with recent vascular events particularly in males. This may be because having a recent cardiac event (CA/TIA) causes anxiety and symptoms of agitation and aggression, rather than acting as a remote causative effect.

We found a positive association between TBI and aggression in AD males, to our knowledge previously unreported. TBI and aggression in the general population has been found to positively associate with one another, as described by Tateno et al. [9]. A number of papers have also previously found a positive association between TBI and AD. In particular, a study by Nemetz et al. found that TBI decreases the time to onset of AD [10].

Clinically diagnosed LBDS was greater in A(+)IAD females but it was not confirmed on testing for alpha-synuclein presence. This finding highlights the discrepancy between clinical and pathological diagnosis in dementia, as we and others have shown [10, 11].

The presence of phosphorylated TDP-43 deposits was greater in A(+). TDP-43 is one of two common substrates required for pathological diagnosis of FTD, but it is also present in the limbic regions of many AD patients; Ortiz et al. found that 20% of AD cases express TDP-43 in the hippocampus [12]. To our knowledge this is the first time that TDP-43 has been found to associate with agitation/aggression in AD. The distribution of p-TDP-43 in relation to A(+) would be of interest in future studies. Of marginal interest, the clinical

diagnosis of FTD, regardless of pathology was also associated with A(+). The alternative substrate of FTD, tauopathy, did not associate with A(+)AD.

Although agitation/aggression associated with presence of psychoses, their risk factors are different. For example, Lewy body pathology and vascular risk factors have been found to increase the development of psychoses (hallucinations and delusions) in AD [2].

A specific limitation in this study that must be noted is that presence of agitation/aggression was assessed by one question: “Is the patient stubborn and resistive to help from others?”. Therefore, this is not a comprehensive assessment of agitation/aggression in AD. The use of multiple univariate tests may inflate the rate of type I error. Following a tradition at this exploratory stage, we have not corrected for multiple testing. Precisely for this reason we kept the statistics simple and did not include covariate analysis [13]. We chose not to exclude patients based presence of coexisting pathologies, and thus the sample does not represent “pure AD”, but is closer to clinical reality with multiple pathologies. Risk factor variables are based on caregiver report rather than objective data. Variable reporting from AD centers as well as changes in data collection over time may also have affected data output.

Conclusion

In conclusion, agitation/aggression in AD is associated with specific variables/risk factors, some of which are unexpected. Although significance is reached only in some, the trends are present in all subgroups, with the exception of TIA and TDP-43. Expected positive associations include: males, cognitive and functional status, delusions, hallucinations, and depression. Unexpected positive associations include smoking (females; IAD), recent TIA (males; IAD), recent HA/CA (males; IAD), clinical TBI (males; HAD), clinical diagnosis of FTD (males; HAD), and TDP-43 pathology (males; IAD). Unexpected negative associations include education and vascular lesions. Our findings may help on the identification of risk factors for agitation in AD as well as in the management of these patients.

Acknowledgments

The NACC database is funded by NIA/NIH Grant U01 AG016976. NACC data are contributed by the NIA funded ADCs: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Steven Ferris, PhD), P30 AG013854 (PI M. Marsel Mesulam, MD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50AG016573 (PI Frank LaFerla, PhD), P50 AG016570 (PI Marie-Francoise Chesselet, MD, PhD), P50 AG005131 (PI Douglas Galasko, MD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P50 AG005136 (PI Thomas Montine, MD, PhD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P50AG005681 (PI John Morris, MD), and P50 AG047270 (PI Stephen Strittmatter, MD, PhD) [1].

Alzheimer’s Disease Genetic Consortium (ADGC) (NIA/NIH Grant U01 AG032984).

References

1. Beekly DL, Ramos EM, Lee WW, Deitrich WD, Jacka ME, Wu J, Hubbard JL, Koepsell TD, Morris JC, Kukull WA. NIA Alzheimer's Disease Centers. The National Alzheimer's Coordinating Center (NACC) database: The Uniform Data Set. Alzheimer Dis Assoc Disord. 2007; 21:249–258. [PubMed: 17804958]
2. Holmes C, Arranz MJ, Powell JF, Collier DA, Lovestone S. 5-HT2A and 5-HT2c receptor polymorphisms and psychopathology in late onset Alzheimer's disease. Hum Mol Genet. 1998; 7:1507–1509. [PubMed: 9700207]
3. Tekin S, Mega MS, Masterman DM, Chow T, Garakian J, Vinters HV, Cummings JL. Orbitofrontal and anterior cingulate cortex neurofibrillary tangle burden is associated with agitation in Alzheimer's disease. Ann Neurol. 2001; 49:355–361. [PubMed: 11261510]
4. Aarsland D, Cummings JL, Yenner G, Miller B. Relationship of aggressive behavior to other neuropsychiatric symptoms in patients with Alzheimer's disease. Am J Psychiatry. 1996; 153:243–247. [PubMed: 8561206]
5. Berg L. Clinical Dementia Rating (CDR). Psychopharmacol Bull. 1988; 24:637–639. [PubMed: 3249765]
6. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]
7. Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. J Gerontol. 1982; 37:323–329. [PubMed: 7069156]
8. Lopez OL, Becker JT, Sweet RA, Klunk W, Kaufer DI, Saxton J, Habeych M, DeKosky ST. Psychiatric symptoms vary with the severity of dementia in probable Alzheimer's disease. J Neuropsychiatry Clin Neurosci. 2003; 15:346–353. [PubMed: 12928511]
9. Luchsinger JA, Mayeux R. Cardiovascular risk factors and Alzheimer's disease. Curr Atheroscler Rep. 2004; 6:261–266. [PubMed: 15191699]
10. Nemetz PN, Leibson C, Naessens JM, Beard M, Kokmen E, Annegers JF, Kurland LT. Traumatic brain injury and time to onset of Alzheimer's disease: A population-based study. Am J Epidemiol. 1999; 149:32–40. [PubMed: 9883791]
11. Abner EL, Nelson PT, Kryscio RJ, Schmitt FA, Fardo DW, Woltjer RL, Cairns NJ, Yu L, Dodge HH, Xiong C, Masaki K, Tyas SL, Bennett DA, Schneider JA, Arvanitakis Z. Diabetes is associated with cerebrovascular but not Alzheimer's disease neuropathology. Alzheimers Dement. 2016; 12:882–889. [PubMed: 26812281]
12. Ortiz CA, Lin WL, Ahmed Z, Personett D, Davies P, Duara R, Graff-Radford NR, Hutton ML, Dickson DW. TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. Ann Neurol. 2007; 61:435–445. [PubMed: 17469117]
13. Gavett BE, John SE, Gurnani AS, Bussell CA, Saurman JL. The role of Alzheimer's and cerebrovascular pathology in mediating the effects of age, race, and apolipoprotein E genotype on dementia severity in pathologically-confirmed Alzheimer's disease. J Alzheimers Dis. 2015; 49:531–545.

Table 1

Derivation of specific variables included in this paper from the NACC data set [1]

NACC variable	Descriptor
ALCOHOL ABUSE	Alcohol abuse - clinically significant impairment occurring over a 12-month period manifested in one of the following areas: work, driving, legal, or social
Table 2: ALCOHOL ABUSE	Derived from: UDS v3.0 at initial visit
HYPERTEN	UDS Clinical diagnosis of hypertension
Table 2: HYPERTENSION	
CB (TIA)	Recent transient ischemic attack (TIA)
Table 2: RECENT TIA	Derived from: UDS v3.0
CV (HATT)	Heart attack or cardiac arrest
Table 2: RECENT HA/CA	Derived from: UDS v3.0
BRNINJ (TBI)	Traumatic Brain Injury (TBI)
Table 2: TBI	Derived from: Presumptive etiologic diagnosis of the cognitive disorder – original UDS question
NACC (INF)	Infarcts and lacunes
Table 2: LACUNES & INFARCTS	Derived from: Combination of data on the presence of large cerebral artery infarcts, lacunes (small artery infarcts and/or hemorrhages), and gross infarcts across NP form versions
NP (LINF)	Large arterial infarcts
Table 2: LARGE ARTERIAL INFARCTS	Derived from: Combination of data on the presence of large cerebral artery infarcts, lacunes (small artery infarcts and/or hemorrhages), and gross infarcts across NP Form versions
NACC (AVAS)	Severity of atherosclerosis of the circle of Willis
Table 2: SEV of ATHER in C of W	Derived from: severity of gross findings on NP form
LBDS	Clinical Diagnosis of Lewy Body Dementia Syndrome
Table 2: CLINICAL LBDS	Derived from: UDS v3.0
FTD	Clinical Diagnosis of Fronto-Temporal Dementia
Table 2: CLINICAL FTD	Derived from: UDS v3.0
CDR [5]	Clinical Dementia Rating
Table 2: CDR	Derived from: UDS v3.0
MMSE [6]	Min-Mental State Examination
Table 2: MMSE	Derived from: UDS v3.0
FAQ [7]	Functional Activities Questionnaire
Table 2: FAQ	Derived from: UDS v3.0
DEL	Delusions in the last month
Table 2: DELUSIONS	Derived from: UDS v3.0
HALL	Hallucinations in the last month
Table 2: HALLUCINATIONS	Derived from: UDS v.30
DEPRESSION	Clinical Diagnosis of Depression
Table 2: DEPRESSION	Derived from: UDS v3.0

UDS, clinical diagnosis; NP, pathological diagnosis.

J Alzheimers Dis. Author manuscript; available in PMC 2017 September 21.

Table 2

Risk factors in intermediate and high level Alzheimer's disease patients with and without agitation/aggression. Mean (M) and standard deviation (SD) rounded to the nearest significant digit. (The Independent *t* test was used to determine mean and SD for MWU test calculated variables)

NACC variable	A(+)IAD	*A(−)IAD*	*p* value (<0.05)	NACC variable	A(+)HAD	*A(−)HAD*	*p* value (<0.05)
MALE (N = 257)	N = 62/89 69.66%	N = 88/168 52.38%	0.007 *	**MALE (N = 1459)**	N = 411/724 56.77%	N = 383/735 52.11%	0.074 *
AGE (N = 257)	N = 89 (*M* = 80.80, SD = 8.14)	N = 168 (*M* = 84.60, SD = 9.14)	0.001 **	**AGE (N = 1459)**	N = 724(*M* = 75.80, SD = 10.73)	N = 735 (*M* = 77.56, SD = 10.61)	0.008 **
Male (N = 150)	N = 62(*M* = 80.15, SD = 8.05)	N = 88 (*M* = 82.34, SD = 8.71)	0.216 **	*Male (N = 794)*	N = 411 (*M* = 75.38, SD = 9.88)	N = 383 (*M* = 76.02, SD = 10.20)	0.306 **
Female (N= 107)	N = 27 (*M* = 82.30, SD = 8.32)	N = 80 (*M* = 87.08, SD = 9.00)	0.016 **	*Female (N= 665)*	N = 313(*M* = 76.35, SD = 11.74)	N = 352 (*M* = 78.70, SD = 10.87)	0.010 **
AGE AT DEATH (N = 257)	N = 89 (*M* = 82.15, SD = 8.12)	N = 168 (*M* = 85.86, SD = 8.93)	0.002 **	**AGE OF DEATH (N = 1459)**	N = 724 (*M* = 77.75, SD = 10.69)	N = 735 (*M* = 79.26, SD = 10.50)	0.005 **
Male (N= 150)	N = 62 (*M* = 81.37, SD = 7.95)	N = 88 (*M* = 83.66, SD = 8.49)	0.193 **	*Male (N= 794)*	N = 411 (*M* = 77.10, SD = 9.64)	N = 383(*M* = 77.91, SD = 10.00)	0.181 **
Female (N= 107)	N = 27 (*M* = 83.93, SD = 8.37)	N = 80 (*M* = 88.29, SD = 8.81)	0.030 **	*Female (N= 666)*	N = 313(*M* = 78.60, SD = 11.88)	N = 352 (*M* = 80.74, SD = 10.84)	0.028 **
APOE ε4:l versus 0 (N = 207)	N = 34/71 47.89%	N = 51/136 37.50%	0.149 *	**APOE ε4:l versus 0 (N = 1047)**	N = 295/511 57.73%	N = 311/536 58.02%	0.924 *
APOE ε4:2 versus 0 (N = 135)	N = 4/41 9.76%	N = 9/94 9.57%	0.974 *	**APOE ε4:2 versus 0 (N = 635)**	N= 108/324 33.33%	N = 86/311 27.65%	0.120 *
YEARS OF EDUCATION (N = 252)	N = 88,(*M* = 15.92, SD = 1.98)	(*N* = 164, *M* = 15.45, SD = 3.34)	0.318 **	**YEARS OF EDUCATION (N = 1444)**	N = 715,(*M* = 15.29, SD = 3.25)	N = 729,(*M* = 14.92, SD = 3.16)	0.032 **
Male (N= 146)	N = 62,(*M* = 16.39, SD = 3.06)	N = 84, (*M* = 16.32, SD = 3.32)	0.966 **	*Male (N= 791)*	N = 409, (*M* = 16.06, SD = 3.29)	N = 382,(*M* = 15.68, SD = 2.98)	0.052 **
Female (N = 106)	N = 26,(*M* = 14.81, SD = 2.51)	N = 80, (*M* = 14.53, SD = 3.12)	0.970 **	*Female (N= 653)*	N = 306,(*M* = 14.25, SD = 2.91)	N = 347,(*M* = 14.08, SD = 3.15)	0.511 **
CIGARETTE PACKS / DAY (N = 247)	N = 84(*M* = 1.61, SD = 1.61)	N = 163 (*M* = 1.12, SD=1.48)	0.008 **	**CIGARETTE PACKS / DAY (N = 1357)**	N = 672 (*M* = 1.07, SD = 1.46)	N = 685(*M* =1, SD = 1.35)	0.664 **
Male (N = 143)	N = 59(*M* = 1.76, SD = 1.70)	N = 84(*M* = 1.56, SD=1.65)	0.435 **	*Male (N= 733)*	N = 373 (MR =1.32, SD = 1.60)	N = 360(*M* = 1.23, SD = 1.47)	0.634 **
Female (N= 104)	N = 25(*M* = 1.24, SD = 1.36)	N = 79(*M* = 0.65, SD=1.12)	0.011 **	*Female (N= 624)*	N = 299 (*M* = 0.74, SD = 1.18)	N = 325(*M* = 0.74, SD = 1.15)	0.884 **
YEARS SMOKED (N = 249)	N = 86(*M* = 18.41, SD = 20.67)	N = 163 (*M* = 11.4, SD= 16.76)	0.002 **	**YEARS SMOKED (.N = 1367)**	N = 668(*M* = 11.21, SD = 16.63)	N = 699(*M* = 11.58, SD = 16.92)	0.713 **

NACC variable	A(+)IAD	*A(−)IAD*	*p* value (<0.05)	NACC variable	A(+)HAD	*A(−)HAD*	*p* value (<0.05)
Male (N = 145)	N = 60(*M* = 18.22. SD = 20.04)	N = 85 (*M* = 14.05, SD= 17.06)	0.200 **	*Male (N = 741)*	N = 375 (*M* = 12.76, SD = 16.44)	N = 366(*M* = 12.84, SD = 17.11)	0.907 **
Female (N = 104)	N = 26(*M* = 18.85, SD = 22.47)	N = 78(*M* = 8.51, SD = 16.03)	0.003 **	*Female (N = 626)*	N = 293 (*M* = 9.22, SD = 16.71)	N = 333(MR = 10.19, SD = 16.61)	0.346 **
SMOKED 100 CIGARETTES TOTAL (*N* = 255)	N = 58/88, 65.90%	N = 77/167, 46.10%	0.003 *	SMOKED 100 CIGARETTES TOTAL (*N* = 1433)	N = 334/709, 47.11%	N = 336/724, 49.39%	0.633 *
Male (N= 149)	N = 41/62, 66.13%	N = 51/87, 58.62%	0.353 *	*Male (N= 782)*	N = 221/403, 54.84%	N= 196/379, 51.72%	0.382 *
Female (N= 106)	N= 17/26, 65.38%	N = 26/80, 32.50%	0.003 *	*Female (N= 651)*	N = 115/306, 37.58%	N= 138/345, 40.00%	0.528 *
ALCOHOL ABUSE (*N* = 233)	N = 2/79, 2.53%	N = 2/154, 1.30%	0.493 *	ALCOHOL ABUSE (*N* = 1359)	N = 3/659, 0.46%	N = 7/700, 1.00%	0.24 *
HYPER-TENSION (*N* = 236)	N = 50/83, 60.24%	N = 93/153 60.78%	0.935 *	HYPER-TENSION (*N* = 1335)	N = 326/669, 48.73%	N = 313/666, 47.00%	0.526 *
RECENT TIA (*N* = 254)	N = 14/87, 16.09%	N = 26/167, 15.57%	0.008 *	RECENT TIA (*N* = 1429)	N = 54/708, 7.63%	N = 59/721, 8.18%	0.709 *
Male (N = 149)	N = 9/61, 14.75%	N = 9/88, 10.23%	0.02 *	*Male (N =776)*	N = 36/402, 8.96%	N = 30/374, 8.02%	0.825 *
Female (N = 105)	N = 5/26, 19.23%	N = 17/79, 21.52%	0.625 *	*Female (N= 653)*	N = 18/306, 5.88%	N = 29/347, 8.36%	0.201 *
RECENT HA/CA (*N* = 257)	N = 18/89, 20.22%	N = 24/168, 14.27%	0.006 *	RECENT HA/CA (*N* = 1458)	N = 66/724, 9.12%	N = 62/734, 8.45%	0.677 *
Male (N = 150)	N = 14/62, 22.58%	N = 14/88, 15.91%	0.05 *	*Male (N = 794)*	N = 45/411, 1.09%	N = 42/383, 1.10%	0.856 *
Female (N = 107)	N = 4/27, 14.81%	N = 10/80, 12.50%	0.222 *	*Female (N = 664)*	N = 21/313, 6.71%	N = 20/351,5.70%	0.74 *
TBI (*N* = 257)	N = 0/89, 0.00%	N = 4/168, 2.38%	0.142 *	TBI (*N* = 1459)	N = 15/724, 2.07%	N = 2/735, 0.27%	0.001 *
Male (N = 150)	N = 0/62, 0.00%	N = l/88, 1.14%	0.400 *	*Male (N = 794)*	N = 15/411, 3.65%	N = 2/383, 0.052%	0.002 *
Female (N = 107)	N = 0/27, 0.00%	N = 3/80, 3.75%	0.307 *	*Female (N = 665)*	(*N* = 313) N/A *	(N = 352) N/A *	N/A *

*Chi-squared test.

**(MWU)Mann-Whitney U test. Grey shaded box, non-significant values.

J Alzheimers Dis. Author manuscript; available in PMC 2017 September 21.

J Alzheimers Dis. Author manuscript; available in PMC 2017 September 21.

Table 3

Lesions in intermediate and high level Alzheimer's disease patients with and without agitation/aggression. Mean (M) and standard deviation (SD) rounded to the nearest significant digit (The Independent *t* test was used to determine mean and SD for MWU test calculated variables)

NACC variable	A(+)IAD	*A*(−)*IAD*	*p* value (<0.05)	NACC variable	A(+)HAD	*A*(−)*HAD*	*p* value (<0.05)
LACUNES & INFARCTS (N = 256)	N = 16/89, 17.98%	N = 50/167, 29.94%	0.037 *	**LACUNES & INFARCTS (N = 1454)**	N = 134/723, 18.53%	N = 132/731 18.06%	0.814 *
Male (N = 149)	N = 12/62, 19.35%	N = 26/87, 29.88%	0.146 *	*Male (N = 792)*	N = 77/411, 18.73%	N = 78/381, 20.47%	0.538 *
Female (N = 107)	N = 4/27, 14.81%	N = 24/80, 30.00%	0.121 *	*Female (N = 662)*	N = 57/312, 18.27%	N = 54/350, 15.43%	0.329 *
LARGE ARTERIAL INFARCTS (N = 230)	N = 5/82, 6.10%	N = 23/148, 15.54%	0.036 *	**LARGE ARTERIAL INFARCTS (N = 1146)**	N = 39/579, 6.77%	N = 39/567, 6.88%	0.924 *
Male (N = 133)	N = 4/58, 6.90%	N = 12/75, 16%	0.110 *	*Male (N = 635)*	N = 19/339, 5.60%	N = 23/296, 7.77%	0.273 *
Female (N = 97)	N = 1/24, 4.17%	N = 11/73, 15.07%	0.159 *	*Female (N = 511)*	N = 20/240, 8.33%	N = 16/271, 5.90%	0.284 *
SEV of ATHER in C of W (N = 254)	N = 32/88, 36.36%	N = 70/166, 42.17%	0.369 **	**SEV of ATHER in C of W (N = 1444)**	N = 276/718, 38.44%	N = 318/726, 43.80%	0.038 **
Male (N = 148)	N = 20/61, 32.79%	N = 38/87, 43.68%	0.182 **	*Male (N = 785)*	N = 154/407, 37.84%	N = 164/378, 43.39%	0.114 **
Female (N = 106)	N = 12/27, 44.44%	N = 32/79, 40.51%	0.720 **	*Female (N = 659)*	N = 122/311, 39.23%	N = 154/348, 44.25%	0.192 **

* Chi-squared.

** (MWU) Mann-Whitney U test. Grey shaded box, non-significant values.

Table 4

Co-morbidities in intermediate and high level Alzheimer's disease patients with and without agitation/aggression. Mean (M) and standard deviation (SD) rounded to the nearest significant digit (The Independent *t* test was used to determine mean and SD for MWU test calculated variables)

NACC variable	A(+)IAD	*A(−)IAD*	*p* value (<0.05)	NACC variable	A(+)HAD	*A(−)HAD*	*p* value (<0.05)
TAUOPATHY (N = 128)	N = 3/78, 3.85%	N = 5/136, 3.68%	0.950	**TAUOPATHY (N = 1114)**	N = 18/566, 3.18%	N = 30/548, 5.47%	0.059
CLINICAL LBDS (N = 192)	N = 14/75 18.24%	N = 19/117, 16.24%	0.183 *	**CLINICAL LBDS (N = 1406)**	N = 72/709, 10.16%	N = 45/697, 6.46%	0.012 *
Male (N = 118)	N = 9/52, 17.31%	N = 13/66, 19.70%	0.741 *	*Male (N = 765)*	N = 46/401, 11.47%	N = 29/364, 7.97%	0.104 *
Female (N = 74)	N = 9/23, 39.13%	N = 6/51, 11.76%	0.007 *	*Female (N = 641)*	N = 26/308, 8.44%	N = 16/333, 4.80%	0.063 *
ALPHA-SYNUCLEIN (N = 17)	N = 1/4, 25.00%	N = 4/13, 30.77%	0.825 *	**ALPHA-SYNUCLEIN (N = 250)**	N = 35/117, 29.91%	N = 39/133, 29.32%	0.919 *
CLINICAL FTD (N = 230)	N = 5/86, 5.81%	N = 6/144, 4.17%	0.571 *	**CLINICAL FTD (N = 1452)**	N = 43/724, 5.94%	N = 21/728, 2.88%	0.005 *
Male (N = 136)	N = 5/60, 8.33%	N = 4/76, 5.26%	0.475 *	*Male (N = 791)*	N = 30/411,7.30%	N = 14/380, 3.68%	0.027 *
Female (N = 94)	N = 0/26, 0.00%	N = 2/68, 2.94%	0.377 *	*Female (N = 661)*	N = 13/313,4.15%	N = 7/348, 2.01%	0.108 *
P-TDP-43(N = 12)	N = 2/3, 66.67%	N = 4/9, 44.44%	0.505 *	**P-TDP-43(N = 231)**	N = 45/107, 42.06%	N = 30/124, 24.19%	0.004 *
Male (N = 7)	N=l/1, 100%	N = 2/6, 33.33%	0.212 *	*Male (N = 123)*	N = 24/57, 42.11%	N = 15/66, 22.73%	0.021 *
Female (N = 5)	N =l/2, 50%	N = 2/3, 66.66%	0.709 *	*Female (N = 108)*	N = 29/50, 58%	N = 43/58, 74.14%	0.076 *

*Chi-squared.

**(MWU) Mann-Whitney U test. Grey shaded box, non-significant values.

Table 5

Associated symptoms in intermediate and high level Alzheimer's disease patients with and without agitation/aggression. Mean (M) and standard deviation (SD) rounded to the nearest significant digit (The Independent *t* test was used to determine mean and SD for MWU test calculated variables)

NACC variable	A(+)IAD	*A(−)IAD*	*p* value (<0.05)	NACC variable	A(+)HAD	*A(−)HAD*	*p* value (<0.05)
CDR(N = 257)	N = 89 (*M* = 9.02, SD = 5.43)	N=168(*M* = 6.65, SD = 5.642)	0.001 **	**CDR (N = 1459)**	N = 724(*M* = 13.36, SD = 4.74)	N = 735(*M* = 11.68, SD = 5.38)	0.000 **
Male (N= 150)	N = 62 (*M* = 9.18, SD = 5.74)	N = 88(*M* = 6.34, SD = 4.87)	0.003 **	*Male (N = 794)*	N = 411 (*M* = 13.47, SD = 4.71)	N = 383(*M* = 11.42, SD = 5.23)	0.000 **
Female (N= 107)	N = 27 (*M* = 8.65, SD = 4.64)	N = 80(*M* = 7.00, SD = 6.40)	0.083 **	*Female (N = 665)*	N = 313(*M* = 13.21, SD = 4.78)	N = 352(*M* = 11.96, SD = 5.53)	0.010 **
MMSE(N = 211)	N = 66, *M* = 19.17, SD = 7.20)	N = 145, (*M* = 21.59, SD = 7.26)	0.008 **	**MMSE(N = 1039)**	N = 504,(*M* = 11.52, SD = 8.21)	N = 535,(*M* = 14.27, SD = 8.11)	0.000 **
Male (N = 128)	N = 46, (*M* = 19.65, SD = 7.56)	N = 82, (*M* = 21.73, SD = 6.62)	0.000 **	*Male (N=580)*	N = 295,(*M* = 11.02, SD = 8.32)	N = 285,(*M* = 14.26, SD = 7.94)	0.000 **
Female (N = 83)	N = 20, (*M* = 18.05, SD = 6.33)	N = 63, (*M* = 21.40, SD = 8.07)	0.022 **	*Female (N = 459*	N = 209,(*M* = 12.23, SD = 8.03)	N = 250,(*M* = 14.28, SD = 8.31)	0.014 **
FAQ (N = 250)	N = 87, (*M* = 22.38, SD = 9.52)	N = 163, (*M* = 16.42, SD = 11.13)	0.000 **	**FAQ (N = 1437)**	N = 718, (*M* = 26.54, SD = 5.58	N = 719, (*M* = 24.35, SD = 7.73)	0.000 **
Male (N = 144)	N = 60, (*M* = 21.97, SD = 9.97)	N = 84,(*M* = 15.43, *N* = 10.62	0.000 **	*Male (N = 782)*	N = 408, (*M* = 26.42, SD = 5.76)	N = 375 (*M* = 24.08, SD = 7.70)	0.000 **
Female (N = 106)	N = 27, (*M* = 23.30, SD = 8.52)	N = 79,(*M* = 17.48, SD = 11.62)	0.032 **	*Female (N = 654)*	N = 310, (*M* = 26.69 SD = 5.33)	N = 344, (*M* = 24.64 SD = 7.77)	0.002 **
DELUSIONS (N = 257)	N = 26/89, 29.21%	N = 26/168, 15.48%	0.000 *	**DELUSIONS (N = 1459)**	N = 382/724, 52.76%	N = 173/735, 23.54%	0.000 *
Male (N = 150)	N = 22/62, 35.48%	N = 12/88, 13.64%	0.002 *	*Male (N= 794)*	N = 207/411, 50.37%	N = 84/383, 21.93%	0.000 *
Female (N = 107)	N = 10/27, 37.04%	N = 14/80, 17.5%	0.035 *	*Female (N = 665)*	N = 175/313, 55.91%	N = 89/352, 25.28%	0.000 *
HALLUCINATIONS (257)	N = 25/89, 28.09%	N = 29/168, 17.26%	0.043 *	**HALLUCIN-ATIONS (N = 1459)**	N = 260/724, 35.91%	N = 139/735, 18.92%	0.000 *
Male (N = 150)	N = 17/62, 24.42%	N = 19/88, 21.6%	0.410 *	*Male (N = 794)*	N = 134/411, 32.60%	N = 73/383, 19.06%	0.000 *
Female (N = 107)	N = 8/27, 29.63%	N = 10/80, 12.5%	0.040 *	*Female (N = 665)*	N = 126/313, 40.26%	N = 66/352, 18.75%	0.000 *
DEPRESSION (N = 257)	N = 30/89, 33.71%	N = 32/168, 19.05%	0.009 *	**DEPRESSION (N = 1459)**	N = 190/724, 24.24%	N = 139/735, 18.91%	0.001 *
Male (N = 150)	N = 21/62, 33.87%	N = 17/88, 19.32%	0.044 *	*Male (N = 794)*	N = 100/411, 24.33%	N = 70/383, 18.28%	0.038 *
Female (N = 107)	N = 9/27, 33.33%	N = 15/80, 18.75%	0.116 *	*Female (N=665)*	N = 90/313, 28.75%	N = 69/352, 19.60%	0.006 *

* Chi-squared test.

** (MWU) Mann-Whitney U test. Grey shaded box, non-significant values.