Title

APOE e4 genotype and cigarette smoking in adults with normal cognition and mild cognitive impairment: a retrospective baseline analysis of a national dataset

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APOE e4 Genotype and Cigarette Smoking in Adults with Normal Cognition and Mild Cognitive Impairment: A Retrospective Baseline Analysis of a National Dataset

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Abstract

Background—APOE e4 genotype is known to be a risk factor for Alzheimer's disease and atherosclerosis. Recently, published evidence has shown that APOE e4 genotype may also be associated with the cessation of cigarette smoking.

Objectives—The aim of this retrospective analysis was to explore whether any past smoking outcomes differed based on APOE e4 genotype in a large national dataset.

Methods—Data were extracted from the National Alzheimer's Coordinating Center's longitudinal Uniform Data Set study. We limited this retrospective baseline analysis to the normal cognition ($n = 2,995$) and mild cognitive impairment ($n = 1,627$) groups that had APOE genotype and smoking data. Since this was an exploratory retrospective analysis, we conducted descriptive analyses on all variables based on APOE e4 genotype. We controlled for demographic, clinical, medication, and neurocognitive data in the analyses.

Results—In both the normal cognition group and the mild cognitive impairment group, e4 carriers and e4 non-carriers did not significantly differ on total years smoked, age when last smoked, and the average # of packs/day smoked during the years they smoked. In both groups, e4 carriers and e4 non-carriers differed on various neurocognitive measures.

Conclusion—These data do not support the recently published evidence of the association between APOE e4 genotype and smoking outcomes.

Scientific Significance—Larger prospective clinical trials are needed to further explore the relationship between APOE genotype and smoking outcomes.

Keywords

APOE; e4; cigarette smoking; neurocognitive; cognitive; mild cognitive impairment

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Introduction

The epsilon-4 (e4) allele of the apolipoprotein E (APOE) gene is known to be a risk factor for Alzheimer's disease (1–4) and atherosclerosis (5). Recently, published evidence has shown that APOE e4 genotype may be associated with the cessation of cigarette smoking (6). Ashare et al. (2012) analyzed data from 917 cigarette smokers of European ancestry across three smoking cessation clinical trials. They hypothesized that e4 carriers exhibit changes in brain structure/function that may lead to reduced cognitive control over behaviors, such as smoking. Among smokers over the age of 60, they found that e4 carriers were less likely to quit smoking and relapsed more quickly to smoking compared with e4 non-carriers. Their study is the first known study to examine the relationship of APOE genotype with cigarette smoking relapse.

Ashare et al.'s exciting findings prompted us to conduct a retrospective baseline analysis of APOE e4 genotype and smoking outcomes in a data set from the National Alzheimer's Coordinating Center (NACC) (7), which serves as a repository for data collected from adults participating in studies at the 29 Alzheimer's Disease Centers throughout the United States. The longitudinal Uniform Data Set (UDS) (8–11) study began in September 2005 and contains demographic, clinical, neurocognitive and genetic data. The UDS sample consists of participants with normal cognition, mild cognitive impairment, and a dementia such as Alzheimer's disease. The aim of this retrospective analysis was to explore whether any past smoking outcomes differed based on APOE e4 genotype.

At this time, we limited this retrospective analysis of the UDS to the normal cognition group ($n = 2,995$) and the mild cognitive impairment group ($n = 1,627$) that had APOE genotype and smoking data. Compared with e4 non-carriers, we hypothesized that e4 carriers (in both the normal cognition group and the mild cognitive impairment group) would have a significantly greater total number of years smoked and a later age when last smoked (i.e., quit). Though this was a retrospective analysis and retrospective analyses have substantial limitations by their very nature (12, 13), we nevertheless felt this was a timely analysis to conduct given Ashare et al.'s new and intriguing findings.

Methods

Study Setting and Measures

Data were extracted from NACC's (7) longitudinal UDS (8–11). Data were contributed by 29 Alzheimer Disease Centers (ADCs) from across the United States. The ADCs conduct clinical and biomedical research on Alzheimer's disease and related disorders. The data collection used for this analysis began in 9/2005 and had a freeze date of 12/1/2012.

The variables in this analysis were from the baseline initial visit packet form (14) when a participant was enrolled in the UDS study. All UDS forms are freely accessible to the public on the NACC website (15). Demographic data (from form A2 and the derived variables form (16)) included age, sex, ethnicity, race, marital status, and living situation. Clinical data (form A5) included cardiovascular disease, cerebrovascular disease, Parkinsonian features, other neurological conditions, medical/metabolic conditions, depression, substance abuse and psychiatric disorders, Hachinski Ischemic score (form B2) (17), and Geriatric Depression Scale (form B6) (18). The derived variables form (16) was used for medication data and APOE genotype. The neurocognitive battery (form C1) included the Mini-Mental State Examination (MMSE) (19), Logical Memory Immediate & Delayed (20), Digit Span Forward & Backward (20), Category Fluency Animals & Vegetables, Trail Making Test Parts A & B, Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol (21), and Boston Naming Test (22).

As of the 12/1/2012 data freeze, the number of participants in the entire longitudinal NACC UDS was 27,196 (23). For this analysis, we only selected those participants who had APOE e4 genotype data collected and who were determined to have either a "normal cognition" or any type of "mild cognitive impairment" final diagnosis (form D1). [Mild cognitive impairment consisted of any of the 4 subtypes: amnestic memory impairment, amnestic memory impairment plus one or more other domains, non-amnestic single domain, non-amnestic multiple domains.] Of those participants, we then only selected those participants who reported any history of cigarette smoking. The cigarette smoking variables for this analysis included the total years smoked, the age when last smoked (i.e., quit), and the average # of packs/day smoked during the years they smoked (categorized in the NACC UDS as "1 cigarette - <½ pack", "½ - < 1 pack", "1 - <1½ packs", "1½ - 2 packs", and " 2 packs"). The final total number of participants with normal cognition was 2,995, and the final total number of participants with any type of mild cognitive impairment was 1,627.

Statistical analysis

Consistent with Ashare et. al. 2012, we categorized participants with no e4 alleles as "e4 non-carriers" and participants with 1 or 2 e4 alleles as "e4 carriers". All analyses were conducted using IBM SPSS Statistics version 20 (Armonk, NY) and SAS version 9.3 (Cary, NC). Since this was an exploratory retrospective analysis, we primarily conducted descriptive analyses on all variables based on APOE e4 genotype and considered p-values < 0.05 as statistically significant. The raw scores on each neurocognitive measure were converted to standardized z-scores using the web-based normative calculator for the UDS (adjusted for age, sex, and years of education) (24). [The online supplementary material section from this previous publication (24) contains a downloadable Microsoft Excel file; the raw score for each neurocognitive measure can be entered into this Excel file, and a z-score is calculated.]

For the main smoking analyses, we initially conducted the analyses without controlling for any variables. Then, to determine if variables that significantly differed between e4 non-carriers and e4 carriers might be the result of confounding by differences between the groups, we added demographic, clinical, medication, and neurocognitive measures using a general linear model, which allowed us to control for any cluster effects by Alzheimer Disease Center. The dependent variable was each of the smoking measures, and we included the variables that significantly different between e4 non-carriers and e4 carriers in the analysis. We also conducted the smoking analyses by age category (18–30, 31–40, 41–50, 51–60, 61–70, 71–80, 81–90, >90); we divided the age categories until age 60 consistent with Ashare et al. 2012, with further 10-year age increments above age 60 due to having a larger sample size than Ashare et al. 2012. For all of the main smoking analyses, we considered p-values < 0.01 as statistically significant due to the number of analyses being conducted.

Parametric and non-parametric analyses were conducted, and non-parametric results are presented where appropriate. We checked each variable for extreme values (defined as a standardized z-score of >3.29 or < −3.29); extreme values were adjusted to the next highest value, and adjusted results are presented when differing from original results. Since there is the potential of missing data when data are being collecting from 29 different ADCs, we present the varying sample size on which every analysis is based.

Results

Normal cognition group

Table 1 presents demographic, clinical and medication data for the normal cognition group. Most participants were in their 70's and female, had approximately 15 years of education, married, and White. e4 carriers were significantly younger than e4 non-carriers. Compared to e4 carriers, significantly more e4 non-carriers were White, Hispanic, living alone, had Parkinsonian features, urinary incontinence, a greater Hachinski Ischemic score, and likely to be taking an antiadrenergic agent, a diuretic, and an antiparkinson medication. Compared to e4 non-carriers, significantly more e4 carriers were Black/African-American, had hypercholesterolemia, and likely to be taking a non-steroidal anti-inflammatory medication. e4 carriers and e4 non-carriers did not significantly differ on any other demographic, clinical or medication variable ($p > 0.05$). Table 2 presents the mean z-scores for the various neurocognitive measures. Most z-scores for both e4 carriers and e4 non-carriers were greater than 0. Compared to e4 non-carriers, e4 carriers performed significantly worse on Logical Memory A (Immediate & Delayed), the Trail making test Part B, and the Boston Naming Test.

Table 3 presents the main smoking outcomes. Though e4 carriers and e4 non-carriers initially differed significantly on total years smoked and age when last smoked, these differences became non-significant once the variables that significantly differed between e4 non-carriers and e4 carriers (Tables 1 and 2) were entered as covariates. e4 carriers and e4 non-carriers did not significantly differ on the average # of packs/day smoked during the years they smoked. We also compared total years smoked, age when last smoked, and the average # of packs/day smoked during the years they smoked between e4 carriers and e4 non-carriers by age category. e4 carriers and e4 non-carriers did not significantly differ on total years smoked, age when last smoked, and the average # of packs/day smoked during the years they smoked in any age category (all values $p > 0.01$; total years smoked and age when last smoked data presented in Table 4).

Mild cognitive impairment group

Table 5 presents demographic, clinical and medication data for the mild cognitive impairment group. Most participants were in their 70's and male, had approximately 15 years of education, married, and White. e4 carriers were significantly younger than e4 non-carriers. Compared to e4 carriers, significantly more e4 non-carriers were Hispanic, living alone, had Parkinsonian features, a greater Hachinski Ischemic score, and likely to be taking a beta-blocker. Compared to e4 non-carriers, significantly more e4 carriers were married, living in a single family residence, had depression within the past 2 years, and likely to be taking a medication meant for Alzheimer's disease. e4 carriers and e4 non-carriers did not significantly differ on any other demographic, clinical or medication variable ($p > 0.05$). Table 6 presents the mean z-scores for the various neurocognitive measures. All z-scores for both e4 carriers and e4 non-carriers were less than 0. Compared to e4 non-carriers, e4 carriers performed significantly worse on the MMSE, Logical Memory A (Immediate & Delayed), and Category Fluency. Compared to e4 carriers, e4 non-carriers performed significantly worse on the Trail making test Part A.

Table 7 presents the main smoking outcomes. e4 carriers and e4 non-carriers did not significantly differ on total years smoked, age when last smoked, and the average # of packs/day smoked during the years they smoked (all values $p > 0.01$). These non-significant results remained even when comparing by age category (all values $p > 0.01$; total years smoked and age when last smoked data presented in Table 8).

Discussion

This report is a retrospective baseline analysis of APOE e4 genotype and smoking outcomes in 2,995 participants with normal cognition and 1,627 participants with mild cognitive impairment, which was prompted by Ashare et al.'s 2012 recent findings (6). Contrary to our hypotheses, e4 carriers and e4 non-carriers in both the normal cognition group and the mild cognitive impairment group did not significantly differ on total years smoked, age when last smoked, and the average # of packs/day smoked during the years they smoked.

Our findings were likely different from Ashare et al. due to several factors. First, the participants in this analysis were not part of a cigarette smoking cessation clinical trial, but rather part of a longitudinal study focusing on cognitively impaired populations. Second, the smoking outcomes relied on recalling details about smoking which occurred decades ago in many cases. For example, recall in the mild cognitive impairment group would most likely be limited by the cognitive impairment, and this may limit the reliability of the smoking variables in the mild cognitive impairment group. The fact that a significant percentage of participants in the mild cognitive impairment group were taking a medication for Alzheimer's disease provides evidence that the cognitive impairment was affecting them enough to warrant such a pharmacologic intervention.

Third, since this was a post-hoc analysis, the original UDS study only included limited variables on substance abuse. We were only able to analyze the smoking outcomes captured in the UDS initial visit forms at baseline. Fourth, the mean age of our sample in both groups was about 25 to 30 years greater than Ashare et al.'s sample. The attitudes on smoking cessation may have varied with the age group, as noted in previous research (25–27). Finally, most of the participants in this analysis had comorbid medical issues, which may have influenced one's length of smoking or motivated one's quit date.

Though we have highlighted several limitations of our analysis, our analysis has some strengths compared to Ashare et al. First, we were able to analyze a much larger sample size (approximately 5 times larger). Second, we had access to a full neurocognitive assessment that confirmed a participant's cognitive status, instead of relying only on self-reported cognitive symptoms. Third, the racial diversity of this sample consisted of Black/African-American and Hispanic individuals, in addition to White individuals. Previous research has shown that race can influence the APOE genotype's effect on cognition (28–30). Finally, we had sex differences in the normal cognition group versus the mild cognitive impairment group, and sex differences are known to influence smoking outcomes (31–33).

We offer some thoughts on what these data may mean. First, perhaps APOE e4 is only relevant in those with a formal diagnosis of nicotine dependence but not in those who are non-dependent smokers [e.g., "chippers" (34)]. Since a measure like the Fagerstrom Test of Nicotine Dependence (FTND) was not used in this dataset, we only know whether the individuals in this analysis were cigarette smokers and not whether they carried a formal diagnosis of nicotine dependence. Ashare et al.'s data included the FTND and individuals with nicotine dependence. Thus, the stage of cigarette smoking might be an issue (35); maybe APOE e4 genotype doesn't matter in cigarette smokers overall, but only matters in those with nicotine dependence.

Next, perhaps APOE e4 and cigarette smoking are interacting indirectly at best and affecting some other clinical outcome, versus directly affecting each other. As an example, previous literature shows that APOE genotype and cigarette smoking interact to affect coronary heart disease risk (36). Maybe these data were not sufficient for capturing such indirect interactions. Finally, variants in genes such as nAChR, CYP2A6, COMT (37–48) — and

many others — have been associated with cigarette smoking. Perhaps APOE e4 is simply not associated with any aspect of cigarette smoking, and other genes are important instead.

Conclusions

These data do not support the overall notion that APOE e4 genotype may be associated with smoking outcomes. Potential future directions include larger prospective clinical trials confirming or refuting our results, exploring other APOE alleles, and confirming detailed smoking histories with an informant. We hope our analysis catalyzes other research groups to explore the relationship between APOE genotype and smoking outcomes in much greater detail.

Acknowledgments

References

1. Small BJ, Rosnick CB, Fratiglioni L, Backman L. Apolipoprotein E and cognitive performance: a meta-analysis. Psychol Aging. 2004; 19(4):592–600. [PubMed: 15584785]

2. Crean S, Ward A, Mercaldi CJ, Collins JM, Cook MN, Baker NL, Arrighi HM. Apolipoprotein E epsilon4 prevalence in Alzheimer's disease patients varies across global populations: a systematic literature review and meta-analysis. Dement Geriatr Cogn Disord. 2011; 31(1):20–30. [PubMed: 21124030]

3. Sadigh-Eteghad S, Talebi M, Farhoudi M. Association of apolipoprotein E epsilon 4 allele with sporadic late onset Alzheimer's disease. A meta-analysis. Neurosciences (Riyadh). 2012; 17(4):321–326. [PubMed: 23022896]

4. Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol. 2013; 9(2):106–118. [PubMed: 23296339]

5. Horejsi B, Ceska R. Apolipoproteins and atherosclerosis. Apolipoprotein E and apolipoprotein(a) as candidate genes of premature development of atherosclerosis. Physiol Res. 2000; 49(Suppl 1):S63–69. [PubMed: 10984073]

6. Ashare RL, Karlawish JH, Wileyto EP, Pinto A, Lerman C. APOE varepsilon4, an Alzheimer's disease susceptibility allele, and smoking cessation. The pharmacogenomics journal. 2012 doi: 10.1038/tpj.2012.49. [Epub ahead of print 12/18/2012.].

7. National Alzheimer's Coordinating Center (NACC). [Accessed 4/15/2013] https://www.alz.washington.edu –

8. Morris JC, Weintraub S, Chui HC, Cummings J, Decarli C, Ferris S, Foster NL, Galasko D, Graff-Radford N, Peskind ER, Beekly D, Ramos EM, Kukull WA. The Uniform Data Set (UDS): clinical and cognitive variables and descriptive data from Alzheimer Disease Centers. Alzheimer Dis Assoc Disord. 2006; 20(4):210–216. [PubMed: 17132964]

9. [Accessed 4/15/2013] Uniform Data Set (NACC). https://www.alz.washington.edu/WEB/study-pop.html –

10. Weintraub S, Salmon D, Mercaldo N, Ferris S, Graff-Radford NR, Chui H, Cummings J, DeCarli C, Foster NL, Galasko D, Peskind E, Dietrich W, Beekly DL, Kukull WA, Morris JC. The

Alzheimer's Disease Centers' Uniform Data Set (UDS): the neuropsychologic test battery. Alzheimer Dis Assoc Disord. 2009; 23(2):91–101. [PubMed: 19474567]

11. Beekly DL, Ramos EM, Lee WW, Deitrich WD, Jacka ME, Wu J, Hubbard JL, Koepsell TD, Morris JC, Kukull WA, Centers NIAAsD. The National Alzheimer's Coordinating Center (NACC) database: the Uniform Data Set. Alzheimer Dis Assoc Disord. 2007; 21(3):249–258. [PubMed: 17804958]

12. Ward RA, Brier ME. Retrospective analyses of large medical databases: what do they tell us? J Am Soc Nephrol. 1999; 10(2):429–432. [PubMed: 10215345]

13. Shi L, Wu EQ, Hodges M, Yu A, Birnbaum H. Retrospective economic and outcomes analyses using non-US databases: a review. Pharmacoeconomics. 2007; 25(7):563–576. [PubMed: 17610337]

14. [Accessed 4/15/2013] Uniform Data Set – Initial Visit Packet (NACC). https://www.alz.washington.edu/NONMEMBER/UDS/DOCS/VER2/ivpfillable.pdf –

15. [Accessed 4/15/2013] Uniform Data Set – Forms and Documentation (NACC). https://www.alz.washington.edu/WEB/forms-uds.html –

16. [Accessed 4/15/2013] Derived Variables (NACC). https://www.alz.washington.edu/WEB/dervar.pdf –

17. Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. Pathological verification of ischemic score in differentiation of dementias. Ann Neurol. 1980; 7(5):486–488. [PubMed: 7396427]

18. Sheikh, JI.; Yesavage, JA. Clinical Gerontology : A Guide to Assessment and Intervention. Haworth Press; New York, NY: 1986. Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version; p. 165-173.

19. 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(3):189–198. [PubMed: 1202204]

20. Wechsler, D. Wechsler Memory Scale-Revised. Psychological Corporation; San Antonio, TX: 1987.

21. Wechsler, D. Manual for the Wechsler Adult Intelligence Scale – Revised. Psychological Corporation; New York, NY: 1981.

22. Kaplan, EF.; Goodglass, H.; Weintraub, S. The Boston Naming Test - Experimental edition. Lea & Febiger; Philadelphia, PA: 1983.

23. [Accessed 4/15/2013] Description of available data (NACC). https://www.alz.washington.edu/WEB/data-descript.html –

24. Shirk SD, Mitchell MB, Shaughnessy LW, Sherman JC, Locascio JJ, Weintraub S, Atri A. A web-based normative calculator for the uniform data set (UDS) neuropsychological test battery. Alzheimers Res Ther. 2011; 3(6):32. [PubMed: 22078663]

25. Kirscht JP, Brock BM, Hawthorne VM. Cigarette smoking and changes in smoking among a cohort of Michigan adults, 1980–82. Am J Public Health. 1987; 77(4):501–502. [PubMed: 3826471]

26. Frank PI, Morris JA, Frank TL, Hazell ML, Hirsch S. Trends in smoking habits: a longitudinal population study. Fam Pract. 2004; 21(1):33–38. [PubMed: 14760041]

27. Hyland A, Li Q, Bauer JE, Giovino GA, Steger C, Cummings KM. Predictors of cessation in a cohort of current and former smokers followed over 13 years. Nicotine Tob Res. 2004; 6(Suppl 3):S363–369. [PubMed: 15799599]

28. Sawyer K, Sachs-Ericsson N, Preacher KJ, Blazer DG. Racial differences in the influence of the APOE epsilon 4 allele on cognitive decline in a sample of community-dwelling older adults. Gerontology. 2009; 55(1):32–40. [PubMed: 18525196]

29. Romero LJ, Schuyler M, Kamboh MI, Qualls C, LaRue A, Liang HC, Rhyne R. The APO E4 allele and cognition in New Mexico Hispanic elderly. Ethn Dis. 2002; 12(2):235–241. [PubMed: 12019933]

30. Tang MX, Maestre G, Tsai WY, Liu XH, Feng L, Chung WY, Chun M, Schofield P, Stern Y, Tycko B, Mayeux R. Relative risk of Alzheimer disease and age-at-onset distributions, based on APOE genotypes among elderly African Americans, Caucasians, and Hispanics in New York City. Am J Hum Genet. 1996; 58(3):574–584. [PubMed: 8644717]

31. Birmpili E, Katsiki N, Malhotra A, Dimopoulou E, Mikhailidis DP, Tsiligiroglou-Fachantidou A. Gender and Socio-economic Differences in Daily Smoking and Smoking Cessation Among Adult Residents in a Greek Rural Area. Open Cardiovasc Med J. 2012; 6:15–21. [PubMed: 22435078]

32. Johnson JL, Ratner PA, Malchy LA, Okoli CT, Procyshyn RM, Bottorff JL, Groening M, Schultz A, Osborne M. Gender-specific profiles of tobacco use among non-institutionalized people with serious mental illness. BMC Psychiatry. 2010; 10:101. [PubMed: 21118563]

33. Iliceto P, Fino E, Pasquariello S, D'Angelo Di Paola ME, Enea D. Predictors of success in smoking cessation among Italian adults motivated to quit. J Subst Abuse Treat. 2013; 44(5):534–540. [PubMed: 23312770]

34. Shiffman S, Kassel JD, Paty J, Gnys M, Zettler-Segal M. Smoking typology profiles of chippers and regular smokers. J Subst Abuse. 1994; 6(1):21–35. [PubMed: 8081107]

35. Lessov-Schlaggar CN, Pergadia ML, Khroyan TV, Swan GE. Genetics of nicotine dependence and pharmacotherapy. Biochem Pharmacol. 2008; 75(1):178–195. [PubMed: 17888884]

36. Gustavsson J, Mehlig K, Leander K, Strandhagen E, Bjorck L, Thelle DS, Lissner L, Blennow K, Zetterberg H, Nyberg F. Interaction of apolipoprotein E genotype with smoking and physical inactivity on coronary heart disease risk in men and women. Atherosclerosis. 2012; 220(2):486–492. [PubMed: 22071360]

37. Kortmann GL, Dobler CJ, Bizarro L, Bau CH. Pharmacogenetics of smoking cessation therapy. Am J Med Genet B Neuropsychiatr Genet. 2010; 153B(1):17–28. [PubMed: 19475569]

38. David SP, Johnstone EC, Churchman M, Aveyard P, Murphy MF, Munafo MR. Pharmacogenetics of smoking cessation in general practice: results from the patch II and patch in practice trials. Nicotine Tob Res. 2011; 13(3):157–167. [PubMed: 21330274]

39. Mwenifumbo JC, Tyndale RF. Molecular genetics of nicotine metabolism. Handb Exp Pharmacol. 2009; 192:235–259. [PubMed: 19184652]

40. Wang JC, Kapoor M, Goate AM. The genetics of substance dependence. Annu Rev Genomics Hum Genet. 2012; 13:241–261. [PubMed: 22703173]

41. Benowitz NL. Nicotine addiction. N Engl J Med. 2010; 362(24):2295–2303. [PubMed: 20554984]

42. Lazary J, Dome P, Faludi G. Genetic and pharmacogenomic data on smoking: the bigger sample size, the less reliable phenotype? A critical review. Neuropsychopharmacol Hung. 2011; 13(1):7–13. [PubMed: 21451187]

43. Iwahashi K, Aoki J. A review of smoking behavior and smokers evidence (chemical modification, inducing nicotine metabolism, and individual variations by genotype: dopaminergic function and personality traits). Drug Chem Toxicol. 2009; 32(4):301–306. [PubMed: 19793020]

44. Al Koudsi N, Tyndale RF. Genetic influences on smoking: a brief review. Ther Drug Monit. 2005; 27(6):704–709. [PubMed: 16404798]

45. Munafo MR, Johnstone EC. Genes and cigarette smoking. Addiction. 2008; 103(6):893–904. [PubMed: 18190672]

46. Li MD. The genetics of nicotine dependence. Curr Psychiatry Rep. 2006; 8(2):158–164. [PubMed: 16539894]

47. Davies GE, Soundy TJ. The genetics of smoking and nicotine addiction. S D Med. 2009; (Spec No):43–49. [PubMed: 19363894]

48. Schnoll RA, Johnson TA, Lerman C. Genetics and smoking behavior. Curr Psychiatry Rep. 2007; 9(5):349–357. [PubMed: 17915073]

Table 1

Demographic, clinical and medication data[a] at the baseline visit – Normal cognition group based on final diagnosis.

	No APOE e4 alleles	1 or 2 APOE e4 alleles	Significance between groups
(checkered box)	Mean (S.D.[b]) or %		
Age (years)	73.4 (9.8) ($n = 2131$)	70.4 (9.7) ($n = 864$)	$U^c = 755{,}070.0$, $z = -7.72$, $p < 0.0001$
Years of Education	15.4 (3.0) ($n = 2118$)	15.6 (2.9) ($n = 857$)	$U = 934{,}450.5$, $z = 1.29$, $p = 0.20$
Female	59.7% (from total n of 2131)	60.9% (from total n of 864)	$\chi^2(1) = 0.36$, $p = 0.55$
White	86.1% (from total n of 2122)	81.9% (from total n of 861)	$\chi^2(1) = 8.49$, $p = 0.004$
Black or African-American	10.0% (from total n of 2122)	13.2% (from total n of 861)	$\chi^2(1) = 644$, $p = 0.01$
Hispanic	5.1% (from total n of 2125)	2.7% (from total n of 862)	$\chi^2(1) = 8.80$, $p = 0.003$
Married	56.1% (from total n of 2103)	59.0% (from total n of 860)	$\chi^2(1) = 2.08$, $p = 0.15$
Living alone	36.7% (from total n of 2120)	31.6% (from total n of 862)	$\chi^2(1) = 6.98$, $p = 0.008$
Parkinsonian features	2.3% (from total n of 2126)	0.7% (from total n of 863)	$\chi^2(2) = 8.45$, $p = 0.004$
Hypercholesterolemia	45.6% (from total n of 2106)	51.7% (from total n of 847)	$\chi^2(2) = 11.33$, $p = 0.003$
Urinary incontinence	11.8% (from total n of 2126)	8.6% (from total n of 863)	$\chi^2(2) = 6.53$, $p = 0.04$
Hachinski Ischemic score	0.77 (1.09) ($n = 2051$)	0.68 (1.15) ($n = 840$)	$U = 804{,}552.5$, $z = -3.10$, $p = 0.002$
Antiadrenergic agent	8.4% (from total n of 2099)	6.0% (from total n of 853)	$\chi^2(1) = 5.12$, $p = 0.02$
Diuretic	19.4% (from total n of 2099)	16.2% (from total n of 853)	$\chi^2(1) = 4.16$, $p = 0.04$
Non-steroidal anti-inflammatory medication	26.4% (from total n of 2099)	31.2% (from total n of 853)	$\chi^2(1) = 6.94$, $p = 0.008$
Antiparkinson medication	3.5% (from total n of 2099)	1.2% (from total n of 853)	$\chi^2(1) = 11.80$, $p = 0.001$

[a] Sample sizes vary due to missing data in the dataset.

[b] S.D. = standard deviation

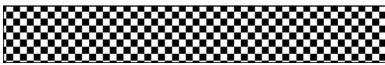[c] U = Mann-Whitney test, with corresponding z-statistic

Table 2

Neurocogmtive data[a] at the baseline visit – Normal cognition group based on final diagnosis.

▓▓▓▓▓▓▓▓▓▓▓▓	No APOE e4 alleles	1 or 2 APOE e4 alleles	Significance between z-scores of groups
	Mean (S.D.) of *z*-score		
MMSE Total Score	0.45 (1.10) (*n* = 2032)	0.36 (1.23) (*n* = 824)	*t*(1382.76) = 1.83, *p* = 0.07
Logical Memory A: Immediate – Story units recalled	0.38 (1.03) (*n* = 1999)	0.26 (1.04) (*n* = 810)	*t*(2807) = 2.60, *p* = 0.009
Logical Memory A: Delayed – Story units recalled	0.39 (1.02) (*n* = 1983)	0.30 (0.99) (*n* = 801)	*t*(2782) = 2.12, *p* = 0.03
Digit Span Forward: Length	−0.01 (0.97) (*n* = 2002)	−0.03 (0.98) (*n* = 809)	*t*(2809) = 0.29, *p* = 0.77
Digit Span Backward: Length	0.17 (1.02) (*n* = 2004)	0.09 (1.03) (*n* = 810)	*t*(2812) = 1.76, *p* = 0.08
Category Fluency: Total # of animals named in 60 seconds	0.01 (0.97) (*n* = 2025)	−0.03 (1.02) (*n* = 818)	*t*(2841) = 0.99, *p* = 0.32
Category Fluency: Total # of vegetables named in 60 seconds	0.93 (1.19) (*n* = 2003)	0.87 (1.23) (*n* = 808)	*t*(2809) = 1.15, *p* = 0.25
Trail making test – Part A – Total # of seconds to complete	−0.06 (0.99) (*n* = 1994)	−0.11 (1.06) (*n* = 815)	*t*(2807) = 1.17, *p* = 0.24
Trail making test – Part B – Total # of seconds to complete	−0.10 (1.0) (*n* = 1982)	−0.20 (1.02) (*n* = 810)	*t*(2790) = 2.58, *p* = 0.01
WAIS-Digit Symbol – Total # of items correctly completed in 90 seconds	0.34 (1.03) (*n* = 1885)	0.31 (1.04) (*n* = 772)	*t*(2655) = 0.56, *p* = 0.57
Boston Naming Test – 30 Odd-numbered items total score	−0.21 (0.91) (*n* = 1993)	−0.30 (0.95) (*n* = 810)	*t*(2801) = 2.33, *p* = 0.02

[a]Sample sizes vary due to missing data in the dataset.

Table 3

Smoking data[a] at the baseline visit – Normal cognition group based on final diagnosis.

		No APOE e4 alleles	1 or 2 APOE e4 alleles	Significance between groups
		Mean (S.D.) or %		
Total years smoked		23.0 (15.2) (n = 2093)	21.7 (15.0) (n = 837)	U = 833,007.50, z = −2.08, p = 0.038
Age when last smoked (i.e., quit)		42.6 (14.0) (n = 1883)	41.0 (13.8) (n = 753)	U = 662,323.50, z = −2.64, p = 0.008
Average # of packs/day smoked when participants smoked[b]	1 cigarette – <½ pack	33.6%	35.2%	$\chi^2(4)$ = 4.69, p = 0.32
	½ – < 1 pack	31.0%	32.0%	
	1 – <1½ packs	18.0%	17.3%	
	1½ – 2 packs	8.0%	8.4%	
	2 packs	9.3%	7.0%	
Total years smoked[c]		22.7 (0.34) (n = 1824)	22.1 (0.54) (n = 737)	p = 0.25
Age when last smoked[d]		42.2 (0.33) (n = 1642)	41.7 (0.52) (n = 670)	p = 0.35

[a]Sample sizes vary due to missing data in the dataset.

[b]"No APOE e4 alleles" total n = 2045; "1 or 2 APOE e4 alleles" total n = 830

[c]Means/standard errors are adjusted for all of the following covariates which were different between the groups (Tables 1 and 2): Age, White, Black or African-American, Hispanic, Living alone, Parkinsonian features, Hypercholesterolemia, Urinary incontinence, Hachinski Ischemic score, Antiadrenergic agent, Diuretic, Non-steroidal anti-inflammatory medication, Antiparkinson medication, Logical Memory A: Immediate, Logical Memory A: Delayed, Trail making test Part B, Boston Naming Test.

[d]Means/standard errors are adjusted for all of the following covariates which were different between the groups (Tables 1 and 2): Age, White, Black or African-American, Hispanic, Living alone, Parkinsonian features, Hypercholesterolemia, Urinary incontinence, Hachinski Ischemic score, Antiadrenergic agent, Diuretic, Non-steroidal anti-inflammatory medication, Antiparkinson medication, Logical Memory A: Immediate, Logical Memory A: Delayed, Trail making test Part B, Boston Naming Test.

Table 4

"Total years smoked" and "Age when last smoked" data[a] by age category at the baseline visit – Normal cognition group based on final diagnosis.

		No APOE e4 alleles	1 or 2 APOE e4 alleles	
		Mean (S.D.)		Significance between groups
Total years smoked	Age 18–30	6.4 (3.9) ($n = 7$)	7.0 (2.6) ($n = 3$)	$t(8) = -0.23$, $p = 0.82$
	Age 31–40	11.8 (7.5) ($n = 4$)	5.0 (1.0) ($n = 3$)	$t(5) = 1.52$, $p = 0.19$
	Age 41–50	14.3 (10.2) ($n = 20$)	14.4 (8.2) ($n = 9$)	$U = 91.5$, $z = 0.071$, $p = 0.95$
	Age 51–60	17.5 (13.6) ($n = 133$)	17.2 (12.7) ($n = 92$)	$U = 6,115.0$, $z = -0.006$, $p = 1.00$
	Age 61–70	20.1 (13.8) ($n = 618$)	20.5 (13.5) ($n = 330$)	$U = 104,480.5$, $z = 0.63$, $p = 0.53$
	Age 71–80	24.5 (15.2) ($n = 816$)	22.6 (15.7) ($n = 265$)	$U = 99,702.5$, $z = -1.91$, $p = 0.056$
	Age 81–90	26.1 (16.0) ($n = 431$)	26.2 (16.6) ($n = 127$)	$U = 27,352.0$, $z = -0.01$, $p = 1.00$
	Age > 90	27.1 (18.8) ($n = 64$)	41.5 (24.6) ($n = 8$)	$U = 359.0$, $z = 1.85$, $p = 0.064$
Age when last smoked	Age 18–30	23.3 (3.5) ($n = 3$)	24.5 (2.1) ($n = 2$)	$t(3) = -0.41$, $p = 0.71$
	Age 31–40	24.5 (9.2) ($n = 2$)	25.7 (5.5) ($n = 3$)	$t(3) = -0.18$, $p = 0.87$
	Age 41–50	30.5 (8.3) ($n = 13$)	30.4 (7.8) ($n = 7$)	$t(18) = 0.029$, $p = 0.98$
	Age 51–60	34.5 (11.7) ($n = 98$)	34.1 (11.6) ($n = 73$)	$U = 3,492.5$, $z = -0.26$, $p = 0.79$
	Age 61–70	39.0 (12.6) ($n = 559$)	40.0 (12.8) ($n = 303$)	$U = 88,296.5$, $z = 1.03$, $p = 0.30$
	Age 71–80	44.0 (13.7) ($n = 741$)	41.9 (13.9) ($n = 243$)	$U = 81,958.5$, $z = -2.10$, $p = 0.036$
	Age 81–90	46.7 (14.2) ($n = 405$)	46.6 (14.9) ($n = 116$)	$U = 23,236.5$, $z = -0.18$, $p = 0.86$
	Age > 90	48.5 (16.2) ($n = 62$)	58.0 (6.7) ($n = 6$)	$t(11.9) = -2.8$, $p = 0.018$

[a]Sample sizes vary due to missing data in the dataset.

Table 5

Demographic, clinical and medication data[a] at the baseline visit – Mild cognitive impairment group based on final diagnosis.

	No APOE e4 alleles	1 or 2 APOE e4 alleles	Significance between groups
	Mean (S.D.) or %		
Age (years)	74.5 (9.9) ($n = 928$)	73.2 (8.0) ($n = 699$)	$U = 288,707.0$, $z = -3.80$, $p < 0.0001$
Years of Education	14.6 (3.5) ($n = 926$)	15.0 (3.2) ($n = 695$)	$U = 335,822.0$, $z = 1.53$, $p = 0.13$
Female	43.2% (from total n of 928)	43.9% (from total n of 699)	$\chi^2(1) = 0.08$, $p = 0.78$
White	82.9% (from total n of 925)	82.9% (from total n of 696)	$\chi^2(1) < 0.001$, $p = 0.99$
Black or African-American	10.9% (from total n of 925)	13.1% (from total n of 696)	$\chi^2(1) = 1.77$, $p = 0.18$
Hispanic	8.3% (from total n of 926)	3.6% (from total n of 698)	$\chi^2(1) = 15.15$, $p < 0.0001$
Married	61.7% (from total n of 924)	71.3% (from total n of 697)	$\chi^2(1) = 16.3$, $p < 0.0001$
Living alone	26.9% (from total n of 926)	21.6% (from total n of 698)	$\chi^2(1) = 5.92$, $p = 0.015$
Living in single family residence	86.4% (from total n of 926)	91.1% (from total n of 698)	$\chi^2(1) = 8.68$, $p = 0.003$
Parkinsonian features	4.8% (from total n of 925)	2.2% (from total n of 695)	$\chi^2(2) = 7.64$, $p = 0.006$
Depression within past 2 years	30.0% (from total n of 922)	35.2 % (from total n of 696)	$\chi^2(2) = 4.83$, $p = 0.03$
Hachinski Ischemic score	1.11 (1.47) ($n = 917$)	0.9 (1.16) ($n = 693$)	$U = 297,206.0$, $z = -2.42$, $p = 0.015$
Beta-blocker	24.9% (from total n of 925)	19.7% (from total n of 696)	$\chi^2(1) = 6.09$, $p = 0.014$
A medication meant for Alzheimer's	19.9% (from total n of 925)	30.7% (from total n of 696)	$\chi^2(1) = 25.3$, $p < 0.001$

[a]Sample sizes vary due to missing data in the dataset.

Table 6

Neurocogmtive data[a] at the baseline visit – Mild cognitive impairment group based on final diagnosis.

▨	No APOE e4 alleles	1 or 2 APOE e4 alleles	Significance between z-scores of groups
	Mean (S.D.) of *z*-score		
MMSE Total Score	−0.94 (1.99) (*n* = 879)	−1.29 (2.01) (*n* = 625)	$t(1529) = 3.34$, *p* = 0.001
Logical Memory A: Immediate – Story units recalled	−0.67 (1.11) (*n* = 860)	−1.11 (1.12) (*n* = 633)	$t(1478) = 7.64$, *p* < 0.001
Logical Memory A: Delayed – Story units recalled	−0.78 (1.15) (*n* = 848)	−1.31 (1.15) (*n* = 632)	$t(1478) = 8.84$, *p* = 0.001
Digit Span Forward: Length	−0.35 (1.04) (*n* = 867)	−0.28 (1.04) (*n* = 645)	$t(1510) = -1.22$, *p* = 0.22
Digit Span Backward: Length	−0.28 (0.96) (*n* = 866)	−0.33 (0.99) (*n* = 645)	$t(1509) = 1.06$, *p* = 0.29
Category Fluency: Total # of animals named in 60 seconds	−0.74 (0.90) (*n* = 871)	−0.73 (0.95) (*n* = 650)	$t(1519) = -0.33$, *p* = 0.74
Category Fluency: Total # of vegetables named in 60 seconds	−0.03 (1.14) (*n* = 862)	−0.18 (1.11) (*n* = 642)	$t(1502) = 2.58$, *p* = 0.01
Trail making test – Part A – Total # of seconds to complete	−0.82 (1.75) (*n* = 860)	−0.58 (1.46) (*n* = 647)	$t(1488.32) = -2.85$, *p* = 0.004
Trail making test – Part B – Total # of seconds to complete	−1.13 (1.63) (*n* = 829)	−1.06 (1.57) (*n* = 632)	$t(1459) = -0.87$, *p* = 0.38
WAIS-Digit Symbol – Total # of items correctly completed in 90 seconds	−0.49 (1.11) (*n* = 829)	−0.52 (1.10) (*n* = 611)	$t(1438) = 0.56$, *p* = 0.58
Boston Naming Test – 30 Odd-numbered items total score	−0.96 (1.53) (*n* = 863)	−0.87 (1.38) (*n* = 639)	$t(1443.84) = -1.10$, *p* = 0.27

[a]Sample sizes vary due to missing data in the dataset.

Table 7

Smoking data[a] at the baseline visit – Mild cognitive impairment group based on final diagnosis.

		No APOE e4 alleles	1 or 2 APOE e4 alleles	Significance between groups
		Mean (S.D.) or %		
Total years smoked		23.9 (15.8) (n = 854)	22.8 (14.5) (n = 641)	U = 265,732.00, z = −0.97, p = 0.33
Age when last smoked (i.e., quit)		43.9 (14.6) (n = 777)	42.4 (13.6) (n = 593)	U = 216,534.50, z = −1.91, p = 0.056
Average # of packs/day smoked when participants smoked[b]	1 cigarette – <½ pack	35.0%	30.6%	χ^2 = 5.24, p = 0.64
	½ – < 1 pack	29.8%	34.0%	
	1 – <1½ packs	17.1%	18.3%	
	1½ – 2 packs	8.6%	8.9%	
	2 packs	9.5%	8.2%	

[a]Sample sizes vary due to missing data in the dataset

[b]"No APOE e4 alleles" total n = 846; "1 or 2 APOE e4 alleles" total n = 638

Table 8

"Total years smoked" and "Age when last smoked" data[a] by age category at the baseline visit – Mild cognitive impairment group based on final diagnosis.

		No APOE e4 alleles	1 or 2 APOE e4 alleles	Significance between groups
		Mean (S.D.)		
Total years smoked	Age 18–30	3.0 ($n = 1$)	None	Not applicable
	Age 31–40	18.0 (1.4) ($n = 2$)	None	Not applicable
	Age 41–50	17.1 (11.3) ($n = 7$)	29.5 (6.4) ($n = 2$)	$t(7) = -1.43$ $p = 0.20$
	Age 51–60	18.0 (13.4) ($n = 68$)	18.5 (13.0) ($n = 38$)	$U = 1,318.0$, $z = 0.17$, $p = 0.86$
	Age 61–70	22.3 (14.1) ($n = 186$)	22.3 (14.0) ($n = 184$)	$U = 17,096.5$, $z = -0.015$, $p = 0.99$
	Age 71–80	25.4 (16.7) ($n = 356$)	23.0 (14.7) ($n = 305$)	$U = 50,346.5$, $z = -1.61$, $p = 0.11$
	Age 81–90	23.3 (15.3) ($n = 200$)	23.9 (15.0) ($n = 103$)	$U = 10,554.0$, $z = 0.35$, $p = 0.73$
	Age > 90	33.8 (16.6) ($n = 34$)	29.8 (15.5) ($n = 9$)	$t(41) = 0.65$ $p = 0.52$
Age when last smoked	Age 18–30	None	None	Not applicable
	Age 31–40	None	None	Not applicable
	Age 41–50	35.2 (12.2) ($n = 5$)	46.5 (5.0) ($n = 2$)	$t(4.74) = -1.75$, $p = 0.14$
	Age 51–60	36.4 (11.8) ($n = 53$)	35.9 (12.6) ($n = 29$)	$U = 755.5$, $z = -0.13$, $p = 0.90$
	Age 61–70	41.9 (12.8) ($n = 168$)	40.1 (11.9) ($n = 166$)	$U = 12,879.5$, $z = -1.21$, $p = 0.23$
	Age 71–80	44.6 (15.1) ($n = 327$)	42.8 (13.6) ($n = 288$)	$U = 43,804.5$, $z = -1.49$, $p = 0.14$
	Age 81–90	45.8 (14.5) ($n = 99$)	45.8 (14.5) ($n = 99$)	$U = 9,783.5$, $z = 0.49$, $p = 0.63$
	Age > 90	55.1 (17.6) ($n = 33$)	52.2 (19.4) ($n = 9$)	$t(40) = 0.42$, $p = 0.68$

[a]Sample sizes vary due to missing data in the dataset.