Published in final edited form as:

Neurobiol Aging. 2009 August ; 30(8): 1327–1328. doi:10.1016/j.neurobiolaging.2007.11.006.

No cross-sectional influence of APOE ϵ 4 dose on clinical tests in Alzheimer's disease

Rochelle E. Tractenberg, Ph.D., M.P.H.^{1,2}, Paul S. Aisen, M.D.¹, Gregory R. Hancock, Ph.D.³, and G. William Rebeck, Ph.D.⁴

¹ Department of Neurology, Georgetown University School of Medicine, Washington, D.C.

²Departments of Biostatistics, Bioinformatics & Biomathematics, and Psychiatry, Georgetown University School of Medicine, Washington, D.C.

³Center for Integrated Latent Variable Research and Department of Measurement, Statistics and Evaluation, University of Maryland, College Park

⁴ Department of Neuroscience, Georgetown University School of Medicine, Washington, D.C.

Abstract

This study sought to determine if there are detectible influences on the symptoms of Alzheimer's disease (AD) from the genetic risk factor for AD, the ϵ 4 allele of apolipoprotein-E (APOE). Using data from two cohorts of AD patients, a cross-sectional latent variable model of AD was tested with three symptom factors explaining variability in the observed variables after taking a general neurological factor into account. No significant influence of ϵ 4 was detected. APOE's effect in AD may occur prior to clinical symptoms, or may simply be more subtle than these instruments can detect.

Keywords

Factor analysis, statistical; Alzheimer's disease; genetic risk factor; cross-sectional analysis.

Introduction

The association between the apolipoprotein-E (APOE) allele and its genotypes and the presence of AD has been established. Of greater controversy is whether there is an important effect of APOE on the common cognitive, functional and behavioral symptoms that are the clinical hallmarks of AD. Tests reflecting an association are rarely, if ever, used in clinical trials for AD. The present report sought to determine if the APOE- ϵ 4 allele has detectible effects on AD clinical trial instrumentation through latent factors in a cross-sectional model of AD (Tractenberg et al. 2006). Control of the measurement error in the model can circumvent the lack of sensitivity that the clinical trial tests exhibit relative to more comprehensive neuropsychological tests.

© 2007 Elsevier Inc. All rights reserved.

Address for correspondence and reprint requests: Rochelle E. Tractenberg 207 Building D 4000 Reservoir Rd., NW Washington, DC 20057 TEL: 202.687.2247 FAX: 202.784.3504 ret7@georgetown.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Methods

The data were collected in two NIH-funded clinical trials (Prednisone study (PR), Aisen et al. 2000; Non-steroidal study (NS), Aisen et al. 2003; descriptive statistics/modeling, Tractenberg et al. 2006).

Materials

The cognitive outcome measures in both trials were the Alzheimer's Disease Assessment Scale – Cognitive, the Clinical Dementia Rating (CDR box scores reflecting cognition (memory, orientation, judgment & problem solving) and function (community affairs, home & hobbies, personal care) were created), and the Mini Mental State Exam. In one study, function was assessed with the Dependency Scale. In the other study, function was assessed with an Activities of Daily Living Inventory, and both cohorts also had CDR functional box scores. Both cohorts had one indicator of general behavioral disturbance and three indicators reflecting psychosis, agitation, and depression. (see Tractenberg et al. 2006 for details).

Procedure

Structural equation modeling was carried out using EQS 6.1 (Multivariate Software, Inc., 2005; Bentler and Wu, 1995). Four models were fit: a model with no effect of $\epsilon 4$; a full effects model where $\epsilon 4$ dose is hypothesized to influence all latent variables; one partial effects model where $\epsilon 4$ dose is hypothesized to influence only the latent general neurological status variable and one model with a causal influence of $\epsilon 4$ dose on each of the three symptom-level latent variables. Four robust (Bentler & Wu, 1999) and one standard fit statistics were assessed for each model.

Results

The two cohorts have been described elsewhere (Aisen et al. 2000, Aisen et al. 2003) as has the modeling (Tractenberg et al. 2006). The model with no influence of $\epsilon 4$ fit the data in both cohorts well, and better than any of the other models. Thus, no evidence was found in either cohort supporting effects of APOE in the model of AD symptoms.

Discussion

The present study tested for influence of $\epsilon 4$ dose (0, 1 or 2 alleles) on latent variables; this represents indirect but error free effects (of the allele) on observed scores. Our results suggest that any influence of $\epsilon 4$ dose on general neurological or symptom-specific factors driving performance on instruments that are common in studies of AD (and particularly in clinical trials/studies) is not significant – or detectable - in a cross-sectional model. Appropriate *longitudinal* versions of the models described here might be able to detect an effect.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

This manuscript was based on an internship report completed to partially fulfill the requirements for a Doctoral-level Graduate Certificate in Gerontology at the University of Maryland, College Park Center on Aging (RET). Supported by a Research Starters Grant in Health Outcomes from the Pharmaceutical Researchers and Manufacturers Association of America (PhRMA) Foundation to RET. The data were collected by the Alzheimer's Disease Cooperative Study under NIA Grant U01 AG10483.

References

- Aisen PS, Davis KL, Berg JD, Schafer K, Campbell K, Thomas RG, Weiner MF, Farlow MR, Sano M, Grundman M, Thal LJ. A randomized controlled trial of prednisone in Alzheimer's disease. Alzheimer's Disease Cooperative Study. *Neurology* 2000;54(3):588–593. [PubMed: 10680787]
- Aisen PS, Schafer KA, Grundman M, Pfeiffer E, Sano M, Davis KL, Farlow MR, Jin S, Thomas RG, Thal LJ, Alzheimer's Disease Cooperative Study. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. *JAMA* 2003;289(21):2819–26. [PubMed: 12783912]
- Bentler, PM.; Wu, E. EQS structural equations program manual. Multivariate Software Inc.; Encino, CA: 1995.
- Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling* 1999;6(1):1–55.
- Tractenberg RE, Aisen PS, Weiner MF, Cummings JL, Hancock GR. Independent contributions of neural and 'higher order' deficits to symptoms in Alzheimer's disease: a latent variable approach. *Alzheimer's and Dementia* 2006;2(4):303–313.