Published in final edited form as:
J Am Geriatr Soc. 2008 March ; 56(3): 478–483. doi:10.1111/j.1532-5415.2007.01574.x.

Health-protective and Adverse Effects of the Apolipoprotein E ε2 Allele in Older Males

Alexander M. Kulminski, PhD[*], **Svetlana V. Ukraintseva, PhD**[*], **Konstantin G. Arbeev, PhD**[*], **Kenneth G. Manton, PhD**[†], **Junko Oshima, MD, PhD**[‡], **George M. Martin, MD**[‡], **Dora Il'yasova, PhD**[§], and **Anatoli I. Yashin, PhD**[*]

Corresponding Author: A. Kulminski Center for Population Health and Aging, Duke University Trent Hall, Room 002, Trent Drive, Box 90408, Durham, NC 27708. Fax: (919) 684-3861 E-mail: Alexander.Kulminski@duke.edu. Alternate Corresponding Author: A. Yashin E-mail: aiy@duke.edu.

Author contributions: Drs. Kulminski and Yashin are responsible for study design, the data analyses, and interpretation of the results. Drs. Kulminski, Ukraintseva, Arbeev, and Yashin take responsibility for the data integrity, the accuracy of the analyses, and drafting the manuscript. Drs. Manton, Oshima, and Martin contributed to the final version. Dr Arbeev participated in preparation of the Medicare data for the analyses and contributed to data description. Dr. Il'yasova contributed to the analysis of the cancer-related results. Dr. Kulminski was responsible for statistical analyses.

Financial Disclosure: The research reported in this paper was supported by the grants 5U01-AG-007198, 1R01 AG028259, 1R01-AG-027019 and 5P01-AG-008761 from the National Institute on Aging (NIA).

Conflict of Interest Disclosures: Each co-author asserts no proprietary interest in the results and no financial conflict of interest as shown in the table.

Elements of Financial/Personal Conflicts	*Author 1		Author 2		Author 3		Etc.	
	AMK		SVU		KGA		KGM, JO, GMM, DI, AIY	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		X		X		X		X
Grants/Funds		X		X		X		X
Honoraria		X		X		X		X
Speaker Forum		X		X		X		X
Consultant		X		X		X		X
Stocks		X		X		X		X
Royalties		X		X		X		X
Expert Testimony		X		X		X		X
Board Member		X		X		X		X
Patents		X		X		X		X
Personal Relationship		X		X		X		X

* Authors can be listed by abbreviations of their names.

[*]Center for Population Health and Aging Duke University Population Research Institute and Department of Sociology, Duke University Trent Hall, Room 002, Trent Drive, Box 90408, Durham, NC 27708, USA.

[†]Arts and Sciences, Duke University Trent Hall, Room 010, Trent Drive, Box 90408, Durham, NC 27708, USA.

[‡]Department of Pathology, University of Washington Box 357470, HSB K-543, 1959 NE Pacific Ave, Seattle, WA, 98195-7470, USA.

[§]Department of Community and Family Medicine/Cancer Control and Prevention, Duke University Medical Center, Durham, NC 27710, USA

Abstract

OBJECTIVES: To re-examine a health-protective role of the common Apolipoprotein E (*APOE*) polymorphism focusing on connections between the *APOE* ε2-containing genotypes and impairments in instrumental activities of daily living [IADL] in older (65+) males and females. To examine how these connections may be mediated by diagnosed coronary heart disease (CHD), Alzheimer's disease, colorectal cancer, macular degeneration (MD), and atherosclerosis.

DESIGN: Retrospective cross-sectional study.

SETTING: The unique disability-focused data from a genetic sub-sample of the 1999 National Long Term Care Survey linked with Medicare service use files.

PARTICIPANTS: 1733 genotyped individuals interviewed on IADL disabilities.

MEASUREMENTS: Indicators of IADL impairments, five geriatric disorders, and ε2-containing genotypes.

RESULTS: The ε2/3 genotype is a major contributor to adverse associations between the ε2 allele and IADL disability in males [Odds Ratio (OR)=3.09, Confidence Interval (CI)=1.53-6.26)]. It shows, however, significant protective effects for CHD (OR=0.55, CI=0.33-0.92), while CHD is adversely associated with IADL disability (OR=2.18, CI=1.28-3.72). The presence of five diseases does not significantly alter the adverse association between ε2-containing genotypes and disability. Protective effects of the ε2/3 genotype for CHD (OR=0.52, CI=0.27-0.99) and deleterious effects for IADL (OR=3.50, CI=1.71-7.14) for males hold in multivariate models with both these factors included. No significant associations between the ε2-containing genotypes and IADL are found in females.

CONCLUSIONS: The ε2 allele can play a dual role in males, protecting them against some health disorders, while promoting others. Strong adverse relationships with disability suggest that ε2-containing genotypes can be unfavorable factors for the health/well-being of aging males.

Keywords

Apolipoprotein E; cardiovascular disease; disability; sex differences

INTRODUCTION

Apolipoprotein E (*APOE*), especially its three common alleles (ε2, ε3, and ε4), is among the most thoroughly studied genetic polymorphisms of *Homo sapiens*. Well established associations of the ε4 allele with Alzheimer's disease [AD] [1,2] suggested adverse effects of this allele on health. Adverse associations of the ε4 allele have also been reported for coronary heart disease [CHD], CHD mortality, and long-term survival [2-4]. There are also suggestions of associations with a range of other disorders (e.g., Parkinson's disease; cognitive decline

[2,4-6]). The *APOE* polymorphism has also been studied for its effect on cholesterol metabolism [2]. These studies have shown that, in general, the ε4 allele increases the level of total and low-density cholesterol, suggesting a mechanism for the negative role of this allele [2,7].

The ε2 allele has been reported to decrease the risks for major geriatric diseases (e.g., AD, CHD) as well as for related mortality in the elderly [1,2]. These observations suggest a health-protective role of this allele. This putative protective mechanism of the ε2 allele may be the result of reduced levels of total and low-density cholesterol [2,7]. An adverse association of the ε2 allele with type III hyperlipoproteinemia (in which very low density lipoproteins [VLDL] and chylomicrons metabolism is affected), however, has been known for decades [2]. Moreover, adverse associations of this allele have been reported for some other late-life diseases (e.g., age-related macular degeneration, (MD), [8,9], colorectal cancer, (CRC), [10]). Carriers of the ε2 allele are less efficient at making and transferring VLDL and chylomicrons from the blood plasma to the liver and are slower to clear dietary fat from their blood compared to carriers of the ε3 or ε4 alleles [1]. Such observations suggest a possible mechanism for deleterious effects of the ε2 allele. These effects may be exaggerated at advanced ages, when metabolism naturally slows. Given the complex role of *APOE* in lipid metabolism [11], additional mechanisms may be playing a role as well (see Section “Discussion and conclusions”).

Thus, the *APOE* polymorphism might be associated with a wide range of both positive and negative health outcomes that impact the functional status. Previous tests of the adverse *APOE* effects have largely focused upon the ε4 allele [12,13]. The ε4 allele was in fact shown to be associated with impaired functional status in a sample of the elderly with normal cognitive function [12]. Later studies, however, failed to demonstrate an association of *APOE* polymorphism with disability in a sample of Italian octo- and nonagenarians [14]. Moreover, the ε4 allele was not a major contributor to the decline in functional status of participants in subjects enrolled in the Duke Established Populations for Epidemiologic Studies of the Elderly (EPESE) [15], although originally non-disabled female carriers of the ε4 allele, exhibited an increased risk of subsequent functional decline [15]. Further analyses of the EPESE data [16], however, showed no association between the *APOE* ε4 status and any of five dimensions of quality of life. Finally, it has recently been shown that the ε4 allele is associated with excessive mobility limitation but not with self-reported functional limitations [13].

This study focuses on the ε2 allele. Its role in health and well-being may be more complex, given findings of both protective and adverse associations with certain geriatric disorders. These findings raise the question of whether the ε2 allele can be considered to be health protective. Given the protective role of the ε2 allele on such major geriatric diseases as CHD and AD, non-immunity against certain other disorders (MD, CRC, atherosclerosis [2,8-10]), and given that disability often summarizes aging-associated health/well-being deterioration [17], this question is addressed by examining connections between the ε2-containing genotypes and impairments in instrumental activities of daily living (IADL) in aged males and females as suggested by the preliminary analyses [18]. The extent to which these connections may be mediated by diagnosed CHD, AD, MD, CRC, and atherosclerosis are also examined. To meet this goal unique disability-focused data on elderly (65+) individuals from a genetic sub-sample (N=1805) of the 1999 National Long Term Care Survey (NLTCS) linked to Medicare service use files [19] is used.

DATA

Study Population

The NLTCS is considered to be one of the best designed surveys to assess chronic disability in the U.S. elderly (65+) individuals [20]. The NLTCS assesses both impairments in activities of daily living (ADL) and IADL [19,21,22]. A two-stage selection interviewing process was used. First, a screening interview assessing chronic disability is given to all members of the sample – except persons who received a community or institutional detailed interview in a prior NLTCS. Those persons reporting on the screen at least one impairment in an ADL or an IADL that had lasted, or was expected to last, 90+ days were then given either an in-person detailed community or institutional interview. Persons who in a prior NLTCS received a detailed interview were automatically given a detailed questionnaire (of the appropriate type determined according to Census criteria on housing type at the time of the personal interview) in the current NLTCS (up to the time of death). The 1994 and 1999 surveys also explicitly included samples of individuals who were designated for detailed interviews before being give a test on disability. Therefore, by the survey design, disabled persons are over-sampled in detailed questionnaires (for details see [19] and references therein) that provides unique opportunity to focus on such vulnerable portion of the older population.

The 1999 NLTCS Sample with *APOE* Information

Biospecimens were collected during 2000-2002 from a sub-sample of participants of the 1999 NLTCS. A total of 2075 blood and buccal cell samples were collected to assess the effects of selected genetic markers on human longevity and physical function. The *APOE* ε2, ε3 and ε4 alleles were determined by the presence or absence of certain restriction sites [23]. Assays were done for 1805 individuals. To test for the reproducibility of the genotyping, 47 peripheral blood samples (1 ε2/ε2; 8 ε2/ε3; 3 ε2/ε4 ; 20 ε3/ε3; 11 ε3/ε4; 4 ε4/ε4) were re-genotyped using two different methods: the original restriction digestion method [23] and an automated sequencing method [24]. The results with all three assays were concordant for each of the genotypes.

For 72 individuals information on disability was missing (N=7) or not collected (N=65, institutionalized population), and, thus, they were excluded from the analysis. Among the other 1733 individuals there were 669 males (38.6%). Mean age of males was 76.7 years (Standard Error, SE: 0.3) and of females 78.5 (SE: 0.2) on the date of interview. The frequencies of the *APOE* genotypes in this sample were: ε2/ε2, N=13, 0.8%; ε2/ε, N=229, 13.2%; ε2/ε4 N=42, 2.4%; ε3/ε3 N=1091, 63.0%; ε3/ε4 N=336, 19.4%; and ε4/ε4, N=22, 1.3%.

Disability

Information on disability is assessed from the NLTCS detail community and institutional questionnaires. Community questionnaire covers 96.4% of the genetic sub-sample and assesses six ADL (eating, getting in/out of bed, getting around inside, getting to the bathroom/using the toilet, dressing, and bathing) and ten IADL (doing heavy work, doing light work, doing laundry, cooking, shopping for groceries, getting around outside, going places outside of walking distance, managing money, making telephone calls, and taking medicines) impairments. Remainder of the sample (N=65) represents institutional population which was interviewed only on six ADL impairments [19] and, thus, was excluded. It has been found that an efficient approach to the analysis of the data is to dichotomize the IADL disability (i.e., to quantify it as either the presence of IADL impairments vs. no disability). Consequently, only this measure is used in the analyses.

Analyses

Sex-specific analysis was performed using logistic regression models adjusted for possible confounders available from self-reports in the NLTCS, i.e., age, race, education, marital status, smoking, drinking, body-mass index, rheumatism or arthritis, diabetes, hypertension, and fractures. CHD (the International Classification of Diseases, Clinical Modification [ICD-9-CM] codes 410-414.9), AD (331), CRC (153-154), MD (362.5-362.57), and atherosclerosis (ATS, 440) were assessed as any of the respective diagnostic codes since 1991 (that is since the time when information on diagnoses from both Medicare Part A and Part B became available). Determinations were made as of the date of interview from linked NLTCS and Medicare service use records.

Major focus of the analysis was on the effect of the ε2/3 genotype. To test the effect modification by the other ε2-containing genotypes, the same analyses were performed for each of six other possible compositions of groups of males and females carrying the ε2 allele. In each analysis dichotomized indices indicating carriers of given genotype(s) were contrasted to carriers of all other genotypes (e.g., the ε2/3 genotype vs. non-ε2/3 genotypes) or to carriers of the ε3/3 genotype. Since results of these analyses were similar, for the final presentation, representative group which includes carriers of the ε2/3 genotype contrasted to all other genotypes was used. Genetic studies involving multiple genes/alleles often require correction for multiple testing [25]. They are necessary to examine for "at least one genetic effect" among the variety of genetic factors subject to testing. Since this is obviously not the case of this study, the correction for multiple testing is not required [26].

To examine the effect of aging-associated disorders (i.e., CHD, AD, MD, CRC, and ATS) on connections between the ε2-containing genotypes and IADL impairments, two aspects were considered. First, we follow the logic [12,13] that the effect of a particular *APOE* allele (the ε2 allele in this study) on disability can be mediated by diseases exhibiting associations with disability and this allele. In other words it was hypothesized that the ε2 allele might increase the risk of certain health disorders (e.g., CRC, MD) while these disorders might be associated with IADL disability. By such analysis each statement of this logic can be tested explicitly and, perhaps, an indirect link between the ε2 allele and IADL disability can be established. Thus, we began by testing the sequence of the associations, i.e., *APOE*↔disease↔IADL.

It might well be the case that such apparently straightforward logic may be simplistic. Other factors (perhaps not as yet known) might mediate adverse associations between the ε2 allele and IADL disability. For example, while perhaps no single disease can result in a statistically significant association, a coherent superposition of a particular subset of disease entities might mediate a process or processes leading to functional disability [17]. Alternatively, certain other phenotypes, (e.g., frailty [27]) might be of special significance in mediating these associations. We therefore have considered the extent to which associations between the ε2 allele and IADL disability (i.e., *APOE*↔IADL) may be modulated by the presence of the selected five diseases and the extent to which these associations remain unexplained.

Finally, the association of the ε2-containing genotypes utilizing each of the seven possible sub-groups of males and females carrying the ε2 allele as dependent variables, with IADL disability and CHD as independent covariates was tested.

RESULTS

Table 1 shows selected descriptive characteristics for the carriers of the most frequent genotypes. It is seen that mean age is roughly the same across genotypes although there is a non-significant trend towards a larger number of males carrying the ε2/3 genotype. The unique focus of the NLTCS on disabled individuals permits to sample large proportions of males and

females with IADL impairments. The most frequent health conditions in this sample are CHD, ATS, and MD.

Analyses of each of the selected health conditions in separate models ("univariate") as well as of all five diseases (i.e., CHD, MD, AD, ATS, and CRC) in a "multivariate" model show that only CHD (males), MD (males), and AD (females) are significantly associated with IADL disability (Table 2). Comparisons of the results for uni- and multi-variate analyses show that these diseases are independently associated with IADL disability.

The analyses show that only CHD and MD are significantly associated with the ε2-containing genotypes. These associations are strongly sex-sensitive (Table 3). For males, significant protective effect of the ε2-containing genotypes on CHD is observed. No such effect is found for females. For females, however, there is significant adverse association between the ε2-containing genotypes and MD, while no such effect is observed for males. The lack of significant effects for other diseases can be partly attributed to insufficient sample size (see Table 1).

Analyses of direct relationships between the ε2-containing genotypes and IADL disability in models adjusted for potential confounders, but without the diseases of interest, show a strong adverse effect for males (Table 4, raw "No"). This adverse association for males is not significantly altered by the diseases (however incorporated, i.e., separately or all together). The odds ratios of the IADL disability for the ε2/3 genotype (Table 4, raw "APOE") are not sensitive to the type of the disorder (i.e., they are similar when the model is adjusted for distinct diseases). The odds ratios of the IADL disability for the diseases are also not significantly altered and resemble those in Table 2. The adverse association is even more pronounced when the ε2/3 genotype is contrasted to carriers of the ε3/3 genotype (e.g., for the models with no diseases OR=4.07, CI: 1.92, 8.60 and with all diseases included OR=4.63, CI: 2.10, 10.2). Nevertheless, adjustment for CHD or/and MD for males tends to increase odds ratios of the IADL disability for the ε2/3 genotype. No significant effect of the ε2-containing genotypes on IADL disability was found for females.

Finally, the analysis shows that adverse association between the ε2-containing genotypes and IADL disability and protective association between the ε2-containing genotypes and CHD for males persist in multivariate models which incorporate both CHD and IADL disability as independent covariates. For instance, for the ε2/3 genotype contrasted to carriers of all other genotypes the odds ratios are: OR=3.50 (CI: 1.71, 7.14) for IADL disability and OR=0.52 (CI: 0.27, 0.99) for CHD which resemble the respective estimates in Table 4 (OR=3.64; CI: 1.71, 7.75) and Table 3 (OR=0.55; CI: 0.33, 0.92).

DISCUSSION AND CONCLUSIONS

Analysis of each statement in the logic connecting the ε2-containing genotypes with IADL disability through the mediating effects of major geriatric diseases (i.e., *APOE*↔disease↔IADL) reveals significant associations of CHD and MD with IADL for males and of Alzheimer's disease with IADL for females (Table 2). Meanwhile, the ε2-containing genotypes are not associated with MD for males while they are significantly associated for females (Table 3). The ε2 allele shows, however, a significant protective effect on CHD for males (but not for females), which is in concordance with other studies [2,3]. No other significant effects are revealed.

These analyses show that such apparent logic of chain associations might not work since analysis of the direct relationship between the ε2-containing genotypes and IADL disability does show a significant male-specific adverse effect, increasing, for instance, the chances of IADL impairments by about 3.1 times in the ε2/3 carriers compared to non-ε2/3 genotypes and

by about 4.1 times compared to ε3/3 genotype in models adjusted for age, race, education, marital status, smoking, drinking, body-mass index, rheumatism or arthritis, diabetes, hypertension, and fractures. This adverse effect is persistent when these models are additionally adjusted either for each of the five geriatric diseases or for all of them. None of those five diseases can explain the adverse association between the ε2-containing genotypes and IADL. None of them significantly modulate this relationship.

These analyses suggest that the role of the ε2 allele can be of a dual nature for males, protecting them against some aging-associated health disorders while promoting others. The strong adverse relationship with IADL disability suggests that the ε2-containing genotypes are rather unfavorable factors for the health/well-being status of older males.

Presence of the association of the ε2 allele with IADL disability separately from its association with certain geriatric disorders suggests at least two plausible explanations. The first can be attributed to possible role of other geriatric disorders which can contribute either individually or complementary to such an association. For instance, the ε2 allele is found to be associated with increased inflammatory response as measured by CRP (but not by TNFalpha and IL-6). It therefore might be associated with chronic inflammatory conditions that involve both elevated CRP levels and impaired IADL, e.g., CRP-associated rheumatoid arthritis, in which higher CRP levels mean greater joint destruction and therefore increased risk of IADL disability [28-31].

The other mechanism may be related to distinct effects of lipid metabolism in an aging organism. For instance, low levels of high-density lipoprotein cholesterol (HDL-C) are found to be significantly associated with disability in the elderly [32-34]. The impact of the *APOE* polymorphism on HDL-C levels can be context-specific and subject to gene-environment and gene-gene interactions such as, for instance, between the *APOE* and the *CETP* loci [7,33]. Specifically, HDL-C concentrations were found to be lower among *APOE* ε2 subjects carrying the B2 allele of the TaqIB polymorphism of the *CETP* gene [7]. Such a pathway linking *APOE* ε2 allele with low HDL-C levels and then with disability might be sex-specific as a result of gene-gene and gene-environment interactions. Moreover, such a pathway may be independent on cardiovascular disease because association between low HDL-C levels and risk of cardiovascular disease may not hold for the elderly [7,32,35].

Despite the robustness of the findings in this study, replicating the adverse associations of the ε2 allele with IADL disabilities in other settings is needed to establish the generality of the conclusions to other populations. Certain limitations of this study should be also noted. The major limitation is the lack of Medicare Part B diagnoses before 1991. Another limitation is that the diagnostic codes may not be highly reliable. However, these limitations are largely offset by the weak effects of diseases with a high prevalence (CHD, MD) on the associations between the ε2-containing genotypes and IADL impairments. Other limitations include the lack of data on lipid profiles in the NLTCS, thus preventing tests of the hypotheses on the mediating roles of components of lipid metabolism [32-34]. On the other hand, several unique features of the present study can be noted, particularly the use of a genetic sample of the NLTCS and the availability of a database which is specifically designed to assess chronic disability in the elderly individuals; the over-sampling of that phenotype has provided substantial increases in statistical power.

ACKNOWLEDGEMENTS

Funding sources and related paper presentations

The research reported in this paper was supported by the grants 5UO1-AG-007198, 1R01 AG028259, 1R01-AG-027019 and 5P01-AG-008761 from the National Institute on Aging (NIA).

Sponsor,s Role: Sponsor institution (NIA) did not played a direct role in the study design, conducts, management, data analysis, review, or authorization for submission.

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Table 1

Descriptive characteristics for the male and female carriers of the most frequent genotypes in the 1999 NLTCS genetic sub-sample.

Factor	Males			Females		
	ε2/3	ε3/3	ε3/4	ε2/3	ε3/3	ε3/4
N	88	424	139	155	703	212
Mean age (SE), yrs	78.1 (0.87)	76.6 (0.34)	76.8 (0.62)	79.5 (0.65)	79.0 (0.30)	78.4 (0.52)
IADL/ND	20/39	47/252	25/72	23/59	95/257	29/79
CHD, yes	38	208	72	77	354	99
AD, yes	2	6	3	2	20	8
ATS, yes	11	65	27	30	153	45
MD, yes	21	79	27	59	178	48
CRC, yes	2	15	5	4	37	14

N=number of individuals; IADL=Instrumental Activities of Daily Living; CHD=Coronary Hearth Disease; AD=Alzheimer's disease; ATS=Atherosclerosis; MD=Macular Degeneration; CRC=Colorectal cancer; SE=standard error; ND=No disability

J Am Geriatr Soc. Author manuscript; available in PMC 2009 September 16.

Table 2

Logistic models of IADL disability for each (univariate) of the five diseases listed in Table 1 and for the set (multivariate) of those five diseases.

Disease	Males		Females	
	univariate	multivariate	univariate	multivariate
CHD	2.18* (1.28, 3.72)	2.16* (1.25, 3.75)	1.32 (0.85, 2.04)	1.31 (0.83, 2.07)
AD	2.80 (0.11, 64.3)	2.27 (0.09, 56.0)	6.65* (1.34, 33.0)	7.01* (1.43, 34.4)
ATS	1.01 (0.47, 2.17)	0.79 (0.35, 1.76)	1.06 (0.59, 1.89)	1.05 (0.58, 1.91)
MD	2.37* (1.25, 4.49)	2.18* (1.14, 4.17)	1.31 (0.79, 2.21)	1.24 (0.73, 2.11)
CRC	0.84 (0.21, 3.44)	0.88 (0.22, 3.55)	1.68 (0.62, 4.52)	1.57 (0.57, 4.29)

Numbers are odds ratios (OR) and 95% Confidence Intervals in parentheses

CHD=Coronary Hearth Disease; AD=Alzheimer's disease; ATS=Atherosclerosis; MD=Macular Degeneration; CRC=Colorectal cancer

The models are adjusted for age, race, education, marital status, smoking, drinking, body-mass index, rheumatism or arthritis, diabetes, hypertension, and fractures.

* denotes significant estimates

Table 3

Logistic models of the ε2/3 genotype contrasted to carriers of all other genotypes for given diseases.

Disease	Males	Females
CHD	0.55* (0.33, 0.92)	0.96 (0.65, 1.41)
AD	0.66 (0.10, 4.30)	0.31 (0.04, 2.43)
ATS	0.73 (0.36, 1.51)	0.85 (0.52, 1.39)
MD	1.00 (0.54, 1.84)	1.77* (1.17, 2.67)
CRC	0.48 (0.10, 2.22)	0.52 (0.18, 1.51)

Numbers are odds ratios (OR) and 95% Confidence Intervals in parentheses

CHD=Coronary Hearth Disease; AD=Alzheimer's disease; ATS=Atherosclerosis; MD=Macular Degeneration; CRC=Colorectal cancer

The models are adjusted for age, race, education, marital status, smoking, drinking, body-mass index, rheumatism or arthritis, diabetes, hypertension, and fractures.

The results are presented for the “univariate” models which include each of the five diseases listed in Table 1. The results of the “multivariate” models which include these diseases altogether resemble the results presented in Table 3 and, thus, are not shown.

*denotes significant estimates

Table 4

Logistic models of IADL disability for the ε2/3 genotype contrasted to carriers of all other genotypes when the diseases are not included (No) and included into the analyses.

Model	Covariate	Males	Females
No	ε2/3	3.09 (1.53, 6.26)	1.20 (0.66, 2.18)
CHD	ε2/3	3.49 (1.67, 7.27)	1.21 (0.66, 2.19)
AD	ε2/3	3.12 (1.54, 6.31)	1.22 (0.66, 2.23)
ATS	ε2/3	3.13 (1.54, 6.35)	1.20 (0.66, 2.19)
MD	ε2/3	3.26 (1.59, 6.70)	1.17 (0.64, 2.13)
CRC	ε2/3	3.09 (1.53, 6.26)	1.20 (0.66, 2.18)
ALL	ε2/3	3.64 (1.71, 7.75)	1.19 (0.65, 2.19)
	CHD	2.31 (1.31, 4.07)	1.31# (0.83, 2.07)
	AD	2.62# (0.11, 65.3)	7.13 (1.44, 35.2)
	ATS	0.84# (0.37, 1.92)	1.05# (0.58, 1.92)
	MD	2.28 (1.18, 4.43)	1.22# (0.72, 2.09)
	CRC	1.00# (0.24, 4.07)	1.57# (0.57, 4.30)

Numbers are odds ratios (OR) and 95% Confidence Intervals in parentheses

CHD=Coronary Hearth Disease; AD=Alzheimer's disease; ATS=Atherosclerosis; MD=Macular Degeneration; CRC=Colorectal cancer; “ALL” denotes model with all five diseases included. For the models which include each disease separately, the associations between given disease and the ε2/3 genotype resemble those as in the model with all diseases included (consequently, the respective ORs are not shown)

The models are adjusted for age, race, education, marital status, smoking, drinking, body-mass index, rheumatism or arthritis, diabetes, hypertension, and fractures.

#denotes non-significant estimates