Title Page

Obesity, apolipoprotein E ε4 and difficulties in activities of daily living among older adults: A six-year follow-up study

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Authors' Statement of Conflict of Interest and Adherence to Ethical Standards

The authors declare that they have no conflict of interest. All procedures, including the informed consent process, were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Obesity, apolipoprotein E ε4 and difficulties in activities of daily living among older adults: A six-year follow-up study

Abstract

Background: Obesity has been associated with increased physical limitations among older adults, although few studies have adjusted for important covariates. There is limited information about the relationship between APOE polymorphisms and physical limitations, and the findings have been inconsistent.

Purpose: This study examined the longitudinal associations of obesity and APOE ε4 with difficulties in activities of daily living (ADLs) over a six-year follow-up period controlling for multiple covariates.

Methods: Data were analyzed from the Social Environment and Biomarkers of Aging Study (SEBAS) in Taiwan collected in 2000 and 2006, involving a cohort of 639 participants (mean age = 66). Body mass index (BMI) was used to define obesity at baseline and the APOE genotype was classified into APOE ε4 carrier and non-carrier status. The combination of basic and instrumental activities of daily living (ADLs and IADLs) was used to define impaired ADLs.

Results: APOE ε4 carriers had greater difficulties in combined ADLs (Incident rate ratio; IRR =1.87, 95 % CI =1.40–2.51) than non-carriers. Obese but not overweight adults had greater difficulties in activities of daily living (IRR =1.59, 95 % CI =1.20–2.10) compared with the normal/underweight group. Obese older adults without APOE ε4 had greater subsequent

difficulties in ADLs than non-obese non-carriers. Among APOE ε4 carriers, obesity was not a significant risk factor for the development of impaired ADLs in older adults, indicating an interaction between genotype and obesity.

Conclusions: The interaction between genotype and obesity phenotype adds new information about the determinants of physical impairment.

Keywords: Physical disability; physical function; mobility; weight status; overweight

Obesity, apolipoprotein E ε4 and difficulties in activities of daily living among older adults: A six-year follow-up study

Introduction

Physical disability, an umbrella term for impairments, activity limitations, or participation restrictions [1], is an important determinant of quality of life in aging [2]. There is abundant evidence that obesity is associated with increased physical disability among older adults [3-5]. Individuals with obesity are at high risk of falls, injuries, and mobility disability [6]. However, few studies have adjusted for important covariates such as physical activity, cognitive function, depressive symptoms, and chronic diseases, even though these may play a role in the relationship between obesity and physical limitations [3, 7]. No research has further included biomarkers in a single study, even though factors such as homocysteine [8] and C-reactive protein (CRP) [9, 10] appear to be associated with physical limitations in older adults.

The role of heredity in physical limitations in aging is also not fully understood. The apolipoprotein E (APOE) gene has been linked to cognitive function and mortality, with the APOE ε4 polymorphism being associated with poor cognitive performance [11, 12] and higher risk of death [13]. Only a few studies have examined the relationship between APOE polymorphisms and physical limitations, and the findings have been inconsistent. Some studies have found significant associations between APOE ε4 and increased difficulties in ADLs [12, 14], while others have not [15-17]. The associations between APOE ε4 carrier status and physical limitations remain unclear. Additionally, no study has examined the associations between the

combination of obesity and APOE ε4 in relation to physical limitations. To fill this gap in the literature, we examined the longitudinal associations of obesity and APOE ε4 with difficulties in activities of daily living among older adults controlling for a number of covariates over a six-year follow-up period.

Methods

Participants

Data used in this study were retrieved from the Social Environment and Biomarkers of Aging Study (SEBAS), a nationally representative longitudinal survey of older adults in Taiwan that included in-home interviews and hospital-based physical examinations. The SEBAS is an extension of the Taiwan Longitudinal Study on Aging (TLSA). The TLSA, beginning in 1989, was a nationally representative cohort of the non-institutionalized population aged 60 and older, with younger refresher cohorts (age 50-66) being added in 1996. The 1999 TLSA included both participants from the 1989 and 1996 TLSA (n=4440). In 2000, participants were randomly selected from the 1999 TLSA for the SEBAS, representing a national sample of Taiwanese adults aged 54 and older [18]. A total of 1497 participants were interviewed and 1023 of them participated in the physical examination in the SEBAS 2000. The second wave of SEBAS was conducted in 2006 with 757 participants (89.5% response rate among survivors) being interviewed and 639 of them completing the hospital-based physical examinations [19]. Our analytic cohort was limited to 639 participants aged 54 to 80 (mean age = 66) with complete information on interviews and medical examinations in both SEBAS surveys. This study was

approved by the Institutional review board at Antai Medical Care Cooperation Antai Tian-Sheng Memorial Hospital in Taiwan.

Both waves of SEBAS included self-reported social-demographic variables, health-related behaviors (e.g. smoking, alcohol consumption, and exercise), health conditions (e.g. chronic disease, activity of daily living, depressive symptoms, cognitive function), and genetic and biological markers from blood and urine samples. More detailed information is provided elsewhere [17, 19, 20].

Measures

Obesity

Height and weight were measured during physical examinations at baseline in 2000. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). The World Health Organization BMI classifications of obesity reflect risks for type 2 diabetes and cardiovascular diseases, which varies among ethnic groups [21]. Therefore, the national criteria of obesity in Taiwan [22] were used to determine underweight, normal, overweight, obesity classifications (obesity ≥27, overweight 24–26.99, normal 18.5–23.99, and underweight <18.5). As prevalence of underweight was very low (2.3%; n=15), the normal and underweight figures were combined and subsequently referred to as ‘normal/underweight’.

Apolipoprotein E genotypes

The technique for determining APOE genotypes has been described in previous studies [23, 24]. Briefly, deoxyribonucleic acid (DNA) was extracted from whole blood and APOE was

genotyped using the polymerase chain reaction (PCR) amplification refractory mutation system and PCR restriction fragment length polymorphism analysis. APOE genotypes were classified into two groups, since this study focused on examining the associations between APOE ε4 and ADL difficulties. Individuals with at least one APOE ε4 allele were defined as APOE ε4 carriers and those without an APOE ε4 allele were defined as non-carriers.

Activities of daily living

Participants were asked to self-report any difficulty they experienced in basic ADLs [25] and instrumental activities of daily living (IADLs) [26] in both 2000 and 2006 surveys. Basic ADLs comprise six types of self-care activities, including dressing and undressing, eating, bathing or showering, walking indoors, getting out of bed and standing up or sitting in a chair, and using the toilet. IADLs include activities of shopping, using public transport, managing money, doing heavy housework, doing light housework, and making phone calls. Each item was rated as not difficult (0), a little difficult (1), very difficult (2), and cannot perform at all (3). A combination of basic ADLs and IADLs has been recommended for the assessment of functional impairment to enhance range and sensitivity of measurement [27] and has been used in previous studies [28, 29]. Therefore, this study used the combination scores of basic ADLs and IADLs (range 0 to 36) to define difficulties in ADLs, with higher scores indicating a higher degree of difficulty. The combination of ADLs and IADLs measured in 2006 was the outcome variable and the combination of baseline ADLs and IADLs measured in 2000 was included as a covariate.

Covariates

Socio-demographic variables included age (<65, 65-74, ≥75), sex, years of schooling (no schooling, 1-6 years, ≥7 years), and marital status (married, all others).

Three health-related behaviors (smoking, alcohol consumption, and exercise) were recoded into binary variables (yes, no). The following questions were asked: “In the past six months, did you smoke?” “In the past six months, did you drink alcohol?” [30]. Participants reported the frequency of exercise in an average week, and responses were categorized into two groups (<3/week, 3+/week), based on the national exercise recommendations of the Taiwan government [31].

Physical and mental health measures included self-reports of current chronic diseases, cognitive function, depressive symptoms and biomarkers assessed during physical examinations. We summed the number of current chronic diseases including high blood pressure, diabetes, heart diseases, stroke, cancer, arthritis, gout, and osteoporosis.

Cognitive functioning was assessed with the Short Portable Mental Status Questionnaire (SPMSQ), which assesses global cognitive function. It requires participants to provide their address, age, date, day of the week, the current president, the last president, mother’s maiden name, and to count backwards from 20 in steps of 3 a total of four times [31]. The number of incorrect responses was summed, with higher scores indicating poor cognitive function. Participants with a score ≥ 4 were categorized as having cognitive impairment [32].

Depressive symptoms were measured using a 10-item Chinese version of the Center for Epidemiologic Studies of Depression Scale (CES-D), which has been validated and used in

previous studies [24, 33, 34]. Each item in the CES-D was rated on a 4-point scale ranging from 0 to 3, with higher total scores representing higher depressive symptoms. Participants with a score ≥ 10 were categorized as having depressive symptoms [35].

Biomarkers included homocysteine and inflammatory markers (high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL 6)), which were obtained from fasting blood samples based on assays described in previous studies [19, 36]. These biomarkers were treated as continuous variables with natural log transformations for skewed distributions in the regression analyses.

These variables were selected as covariates on the basis of documented associations with physical difficulties [3-5, 7-10, 37].

Statistical analyses

Descriptive statistics for all covariates, obesity, and APOE ε4 at baseline were calculated to characterize the participants. An online calculator was used to perform tests of Hardy–Weinberg equilibrium and determine minor allele frequencies (Calculator Hardy-Weinberg equilibrium, 2012). Mann Whitney U test and Kruskal-Wallis tests were used to examine differences in scores of combined ADL difficulties due to the violation of normality. However, comparable results emerged with parametric analyses. Spearman's correlations were conducted to test the univariate associations between continuous variables at baseline and subsequent difficulties in activities of daily living. The scores of combined ADLs were positively skewed and over-dispersed. Thus, negative binomial regressions were conducted to analyze the prospective associations of obesity and APOE ε4 with subsequent difficulties of combined ADLs.

Incident rate ratios (IRRs) (e^B) were reported due to the nonlinearity of the negative binomial distribution in combined ADLs scores.

The data were examined for evidence of multicollinearity with the variance inflation factors (VIF) and tolerance statistics. The VIF > 5 and tolerance values < 0.2 indicate there might be multicollinearity problems (van Vuuren, 2006). In this study, the VIF values ranged from 1.039 to 1.852 and the lowest and highest tolerance values were .540 and .963, suggesting that multicollinearity was not an issue.

Two separate negative binomial regressions were computed. The first regression examined the associations of baseline obesity and APOE ε4 with combined ADL difficulties after six years controlling for socio-demographic variables, cognitive function, health-related behaviors, health status, and difficulties in ADLs at baseline. Then, in order to examine the associations between the combination of obesity and APOE ε4 on subsequent difficulties of activities of daily living, participants were categorized by BMI category across APOE ε4 groups. Since no significant difference was found between overweight and normal/underweight individuals in the first regression analysis, BMI was further grouped into two categories (obese, non-obese). Four groups were then created: APOE ε4 carrier / Obese, APOE ε4 carrier / Non-Obese, Non-carrier / Obese, and Non-carrier / Non-Obese). The second regression was performed to predict subsequent difficulties in combined ADLs by entering this classification with multivariate adjustments.

We conducted sensitivity analyses by separating ADLs and IADLs as outcome variables

in addition to the combined ADLs since the abilities required for ADL and IADLs are distinct in concept. We also carried out sensitivity analyses after excluding those with any difficulties in combined ADLs at baseline. All analyses were conducted using IBM SPSS statistics 22 and a *p*-value less than 0.05 was considered as statistically significant in this study.

Results

Table 1 provides information about characteristics of participants at baseline and the relationship between each variable and the number of combined ADL difficulties at follow-up. The prevalence of obesity and overweight at baseline was 23.3% and 30.2%. The frequencies of ε2, ε3 and ε4 alleles were 8.1, 84.0 and 7.8%, respectively and 15.3% of participants were carriers of the ε4 allele. The distribution of the APOE alleles confirmed to Hardy-Weinberg equilibrium with chi-square=1.93, df=5, and p=0.59.

In the univariate analyses, all variables except for baseline exercise, homocysteine, hsCRP, and APOE ε4 were significantly associated with subsequent difficulties in combined ADLs ($p<0.05$ or greater). Participants who had greater ADL difficulties at follow-up tended to be older, female, less educated, not married, non-smokers, non-drinkers, were obese, had cognitive impairment, depressive symptoms, higher IL 6, and more chronic diseases.

Table 1

Results from the fully adjusted regression models with difficulties in combined ADLs as the outcome are summarized in table 2. APOE ε4 carriers had greater difficulties in combined ADLs (IRR =1.87, 95 % CI =1.40–2.51, $p<0.001$) than non-carriers (model 1). Obese but not

overweight older adults were more likely to have greater ADL difficulties (IRR =1.59, 95 % CI =1.20–2.10, p=0.001) compared with the normal/underweight group. The interaction between obesity and APOE ε4 was also significant (*p*= 0.040). Model 2 shows the association between the combination of obesity and APOE ε4 groups and subsequent difficulties in combined ADLs. Compared with the APOE ε4 non-carrier / non-obese group, the obese and non-obese APOE ε4 carriers and obese APOE ε4 non-carriers had greater difficulties in combined ADLs (IRR =2.35, 95 % CI =1.40–3.96, p=0.001; IRR =2.04, 95 % CI =1.45–2.88, p=<0.001; IRR =1.54, 95 % CI =1.17-2.03, p=0.002, respectively). This pattern is illustrated in Figure 1.

Apart from obesity and APOE ε4, baseline difficulties in activities of daily living significantly predicted difficulties in combined ADLs at follow-up (p<0.001). Participants who were older, female, less educated, had cognitive impairment, depressive symptoms, higher homocysteine, higher IL 6, and more chronic diseases had greater difficulties in combined ADLs than the reference groups (all p< 0.05).

Table 2

Figure 1

The results for separated ADLs and IADLs showed that APOE ε4 carriers had greater subsequent difficulties in ADLs (IRR =3.81, 95 % CI =2.32-6.27, p<0.001) and IADLs (IRR =1.64, 95 % CI =1.22-2.21, p<0.001) than non-carriers. The same trends were found for BMI / APOE ε4 categories in the analyses of ADLs and IADLs as on the main analysis, though effects were stronger for ADLs than IADLs (table 3).

Table 3

The sensitivity analyses that excluded participants with any difficulties in combined ADLs at baseline (table 4) yielded a similar result for APOE ε4, with APOE ε4 carriers having greater subsequent difficulties in combined ADLs (IRR =2.20, 95 % CI =1.53–3.15, p<0.001). The obese and non-obese APOE ε4 carriers and obese APOE ε4 non-carriers also had greater difficulties in combined ADLs compared with the APOE ε4 non-carrier / non-obese group (IRR =2.18, 95 % CI =1.17–4.06, p=0.014; IRR =2.58, 95 % CI =1.69–3.94, p<0.001; IRR =1.48, 95 % CI =1.01-2.16, p=0.042, respectively).

Table 4

Discussion

This longitudinal six-year follow-up study examined obesity, APOE ε4, and difficulties in ADLs controlling for a number of covariates among older adults. The results revealed that APOE ε4 carriers and obese individuals were at higher risk of increased difficulties in combined ADLs. When we further looked at the associations between the combination of obesity and APOE ε4 groups and physical difficulties, obese older adults without APOE ε4 were more likely to have greater subsequent difficulties in ADLs than non-obese non-carriers. Among APOE ε4 carriers, obesity was not a significant predictor of future ADLs. The main analyses combined ADLs and IADLs, but sensitivity analyses indicated that similar patterns were present in both categories of disability.

It has been reported that the presence of APOE ε4 is associated with greater physical

difficulties [12, 14]. However, two studies found no significant associations between APOE ε4 and physical difficulties with the same population of older Taiwanese adults as the one investigated here [16, 17]. One study was cross-sectional [17], while the other involved only three years of follow-up [16]. The number of participants developing difficulties with IADLs and ADLs was small (n= 79 and 35, respectively) and the number of APOE ε4 carriers was even smaller (n=15 and 2, respectively), limiting statistical power. Our study was carried out over six years and the outcome used combined scores of ADLs and IALDs, which might increase sensitivity [27].

This is the first report to reveal an association between the combination of obesity and APOE ε4 and future difficulties in ADLs. Among the APOE ε4 non-carriers, obese older adults were more likely to have greater difficulties in ADLs than non-obese. On the other hand, among the APOE ε4 carriers, obesity might not impact on risk of difficulties in ADLs. One possible explanation may be that APOE ε4 genotype is related to a number of adverse health outcomes, including cognitive impairment [38, 39] and chronic diseases [40-42]. Cognitive impairment has been shown to have an independent impact on ADL [43]. Chronic diseases (such as stroke, diabetes, and arthritis) may also result in physiological impairment, which limits physical abilities [44, 45]. Older adults are particularly susceptible to problems of cognitive impairment and chronic diseases with advancing age, so it is possible that obesity is not a strong predictor among APOE ε4 carriers because of the potential effects of these factors.

Among the covariates, participants who did not smoke or consume alcohol had greater

difficulties in activities of daily living at follow-up in the univarate analyses. However, the results became non-significant in the multivariate models. This study only considered the current smoking and drinking status without identifying former and never smokers or former drinkers. People with poor health are more likely to quit smoking and drinking [28]. Moreover, this study also showed that cognitive impairment, depressive symptoms, more chronic diseases, and higher homocysteine were associated with physical difficulties in older adults.

Although this study extends our understanding of the associations between obesity, APOE ε4, and difficulties of ADLs, it has a number of difficulties. Around 37.5% of participants did not attend the follow-up survey. The main reason for the high attrition rate was a high mortality among this study sample (n=177, 17.3%). No significant differences were found between the dropouts and completers in terms of sex, obesity status, and the presence of APOE ε4. However, the dropouts were more likely to be older, had lower education levels, more chronic diseases, and greater depressive symptoms at baseline. Since these subgroups of population tend to be less healthy, selection bias may lead to underestimation of the association between obesity and difficulties of ADLs. Several other factors might mediate or moderate the effects of APOE genotype or/and obesity on activities of daily living for older adults. We included cognitive function and several health conditions as covariates, and found that the associations of APOE genotype and adiposity were independent of these variables. But we did not test moderation or mediation directly. Furthermore, this observational study cannot establish definitive conclusions about the direction of causality. Obesity was only assessed at baseline, and data were only

available for a follow-up period of six years. Other time intervals or multiple assessments would have been desirable. Subsequent changes in obesity status in the years before follow-up may yield different results. Well-designed randomized control trials and large-scale cohort studies with more repeated measures are encouraged to confirm these findings.

In sum, this study provides evidence that obese older adults without APOE ε4 are more likely to have greater subsequent difficulties in ADLs than non-obese non-carriers. Among the APOE ε4 carriers, obesity did not predict future physical difficulties. The interaction between genotype and obesity phenotype adds new information about the determinants of physical impairments.

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Table 1 Characteristics of participants in 2000 with difficulties in activities of daily living in 2006

Baseline Variables	Characteristics of participants in 2000		Difficulties in activities of daily living in 2006 [a]		
	n	%	n	Mean ± SD	p [b]
Age					<.001
<65	288	45.1%	287	1.03±2.58	
65-74	242	37.9%	241	3.39±6.34	
≥75	109	17.1%	109	7.13±9.26	
Sex					<.001
Female	278	43.5%	277	4.10±6.85	
Male	361	56.5%	360	2.10±5.35	
Years of schooling					<.001
No schooling	188	29.4%	187	5.39±7.95	
1-6 years	272	42.6%	271	2.24±5.08	
7+ years	179	28.0%	179	1.54±4.44	
Marital status					<.001
Others	149	23.3%	148	5.05±7.98	
Married	490	76.7%	489	2.34±5.29	
Smoker					<.001
Yes	139	21.8%	138	1.80±5.18	
No	499	78.2%	498	3.30±6.33	
Alcohol consumer					<.001
Yes	159	25.0%	159	1.75±5.03	
No	477	75.0%	475	3.39±6.41	
Exercise					.824
0-2 times/week	303	47.4%	301	3.18±6.64	
3+ times/week	336	52.6%	336	2.78±5.62	
Cognitive function					<.001
Normal	619	98.3%	617	2.69±5.63	
Abnormal	11	1.7%	11	14.73±13.25	
Depressive symptoms					<.001
Normal	526	83.4%	525	2.18±4.98	
Abnormal	105	16.6%	104	6.52±8.93	
Homocysteine (umol/L)	632	15.39±5.96 [c]	630	ρ=.043 [d]	.286
hsCRP (mg/L) [e]	628	2.66±5.44 [c]	626	ρ=.053 [d]	.184
IL 6 (pg/ml) [f]	610	3.16±3.28 [c]	608	ρ=.132 [d]	.001
N. of Chronic disease	639	0.76±0.90 [c]	637	ρ=.240 [d]	<.001
APOE ε4 [g]					.113
Carrier	98	15.3%	97	3.54±6.63	
Non-carrier	541	84.7%	540	2.87±6.03	
BMI [h]					.023
Obese	149	23.3%	149	4.20±7.59	
Overweight	193	30.2%	193	3.09±6.28	
Normal/underweight	297	46.5%	295	2.27±5.00	
APOE ε4_ BMI					.106
Carrier_Obese	26	4.1%	26	4.58±8.71	
Carrier_Non-obese	72	11.3%	71	3.15±5.70	
Non-carrier_Obese	123	19.2%	123	4.12±7.36	
Non-carrier_Non-obese	418	65.4%	417	2.50±5.53	

a: Mean± SD: 2.97± 6.12 (score range: 0-36); b: Mann Whitney U test or Kruskal-Wallis test; c: Mean ± SD; d: Spearman's correlation; e: high-sensitivity C-reactive protein; f: interleukin-6; g: apolipoprotein E ε4; h: body mass index.

Table 2. Negative binomial regressions for predicting difficulties in activities of daily living

Baseline variables	Model 1 (n=594)			Model 2 (n=594)		
	IRR [a]	95%CI [b]	*p*	IRR [a]	95%CI [b]	*p*
Age			<.001			<.001
<65	.23	.17-.33	<.001	.23	.17-.32	<.001
65-74	.61	.46-.83	.001	.59	.44-.80	.001
≥75	1			1		
Sex			.006			.004
Female	1.51	1.13-2.02		1.53	1.14-2.05	
Male	1			1		
Years of schooling			<.001			<.001
No schooling	2.09	1.52-2.86	<.001	2.04	1.49-2.79	<.001
1-6 years	1.73	1.29-2.31	<.001	1.74	1.30-2.33	<.001
7+ years	1			1		
Marital status			.230			.225
Others	.85	.65-1.11		.85	.65-1.11	
Married	1			1		
Smoker			.890			.943
Yes	1.02	.74-1.42		.99	.71-1.37	
No	1			1		
Alcohol consumer			.145			.134
Yes	.81	.60-1.08		.80	.60-1.07	
No	1			1		
Exercise			.817			.824
0-2 times/week	.97	.78-1.22		.98	.78-1.22	
3+ times/week	1			1		
Cognitive function			.009			.009
Normal	.40	.20-.80		.41	.21-.80	
Abnormal	1			1		
Depressive symptoms			.014			.010
Normal	.70	.52-.93		.68	.51-.91	
Abnormal	1			1		
Homocysteine_log (umol/L)	2.35	1.62-3.41	<.001	2.40	1.65-3.50	<.001
hsCRP_log (mg/L) [c]	.95	.87-1.03	.203	.96	.89-1.04	.333
IL 6_log (pg/ml) [d]	1.22	1.00-1.48	.050	1.20	.99-1.46	.066
N. of Chronic disease	1.14	1.01-1.29	.031	1.15	1.02-1.30	.021
Baseline ADL&IADL [e]	1.19	1.13-1.26	<.001	1.19	1.12-1.26	<.001
APOE ε4 [f]			<.001			
Carrier	1.87	1.40-2.51				
Non-carrier	1					
BMI [g]			.005			
Obese	1.59	1.20-2.10	.001			
Overweight	1.19	.91-1.56	.198			
Normal/underweight	1					
APOE ε4_BMI						<.001
Carrier_Obese				2.35	1.40-3.96	.001
Carrier_Non-obese				2.04	1.45-2.88	<.001
Non-carrier_Obese				1.54	1.17-2.03	.002
Non-carrier_Non-obese				1		

a: Incident rate ratio; b: confidence interval; c: high-sensitivity C-reactive protein; d: interleukin-6; e: basic and instrumental activities of daily living; f: apolipoprotein E ε4; g: body mass index.

Table 3. Sensitivity analyses for predicting future difficulties in activities of daily living (Separating basic and instrumental activities of daily living)

Baseline variables	Model 1			Model 2		
	IRR [a]	95%CI [b]	*p*	IRR [a]	95%CI [b]	*p*
Basic activities of daily living						
APOE ε4 [c]			<.001			
Carrier	3.81	2.32-6.27				
Non-carrier	1					
BMI [d]			<.001			
Obese	4.48	2.79-7.19	<.001			
Overweight	1.33	.80-2.19	.273			
Normal/underweight	1					
APOE ε4_BMI						<.001
Carrier_Obese				11.54	5.08-26.18	<.001
Carrier_Non-obese				4.63	2.49-8.63	<.001
Non-carrier_Obese				4.49	2.80-7.21	<.001
Non-carrier_Non-obese				1		
Instrumental activities of daily living						
APOE ε4 [c]			<.001			
Carrier	1.64	1.22-2.21				
Non-carrier	1					
BMI [d]			.104			
Obese	1.36	1.02-1.81	.034			
Overweight	1.15	.88-1.50	.314			
Normal/underweight	1					
APOE ε4_BMI						.002
Carrier_Obese				1.85	1.09-3.16	.024
Carrier_Non-obese				1.76	1.24-2.49	.002
Non-carrier_Obese				1.33	1.00-1.77	.048
Non-carrier_Non-obese				1		

a: Incident rate ratio; b: confidence interval; c: apolipoprotein E ε4; d: body mass index.

Table 4. Sensitivity analyses for examining subsequent difficulties in activities of daily living
(Excluding any difficulties with activities of daily living at baseline)

Baseline variables	Model1			Model 2		
	IRR [a]	95%CI [b]	*p*	IRR [a]	95%CI [b]	*p*
APOE ε4 [c]			<.001			
Carrier	2.20	1.53-3.15				
Non-carrier	1					
BMI [d]			.092			
Obese	1.47	1.02-2.11	.039			
Overweight	1.30	.92-1.84	.132			
Normal/underweight	1					
APOE ε4_BMI						<.001
Carrier_Obese				2.18	1.17-4.06	.014
Carrier_Non-obese				2.58	1.69-3.94	<.001
Non-carrier_Obese				1.48	1.01-2.16	.042
Non-carrier_Non-obese				1		

a: Incident rate ratio; b: confidence interval; c: apolipoprotein E ε4; d: body mass index.