Effects of the *APOE* ϵ 4 allele and education on cognitive function in Japanese centenarians

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Abstract Apolipoprotein E (*APOE*) ϵ 4 allele and education have been reported to affect the cognitive function in young-old adults. However, the effects and interactions of the ϵ 4 allele and education on cognitive function in very old age, particularly in centenarians, are not well known. We studied 542 Japanese centenarians. Using the data in total of 452 participants (74 men and 378 women, mean age 103.6 ± 3.2 years) who were genotyped and assessed cognitive function with the Mini-Mental States Examination (MMSE), we examined the effects and interactions of the ϵ 4 allele and education on the MMSE score. First, we coded education as three levels: low, middle, and high based on the formal educational levels (analysis 1). Second, to clarify the modifying effect of education, we adopted a new coding for education into two levels, considering a

periodical background (around 1900) of gender differences in educational attainments (analysis 2). In analysis 1, the main effects of the ϵ 4 allele and education on the MMSE score were significant after adjusting for age. Further, there was a significant three-way interaction effect between the ϵ 4 allele, education, and gender on the MMSE. Analysis 2 showed that the modifying effect of the ϵ 4 allele by education was observed only in women with the ϵ 4 allele. These findings suggest that both the *APOE* ϵ 4 allele and education appear to be associated with cognitive function even in centenarians, but the interaction between the ϵ 4 allele and education might depend on gender in this cohort.

Keywords Gene–environment interaction · *APOE* · Cognition · Centenarian

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Cognitive function in late life is a complex phenomenon moderated by genetic and environmental factors and their interactions (Giubilei et al. 2008). The apolipoprotein E (*APOE*) gene and education have been related to cognitive function among young-old adults. *APOE* is located on chromosome 19 and plays a central role of transporting and delivering cholesterol and other lipids or of neuronal repair (Mahley 1988). Among three common alleles— ϵ 2, ϵ 3, and ϵ 4—the ϵ 4 allele might work ineffective repair and protection from neuronal damage (Mahley and Rall 2000). It has been identified as one genetic risk factor for the development of Alzheimer's disease (Raber et al. 2004) and has also been associated with lower cognitive function (Small

et al. 2004) and higher memory complaints (Dik et al. 2001) across the adult life span.

However, whether *APOE* $\epsilon 4$ has an effect on the cognitive function in very old age, such as centenarians, is still controversial. While there was a significant negative association between the $\epsilon 4$ allele and cognitive function among 103 Korean centenarians (Choi et al. 2003), this finding was not observed in 179 Finnish (Sobel et al. 1995) and 33 Japanese centenarians (Asada et al. 1996).

A small sample size would yield such inconsistent results of the *APOE* $\epsilon 4$'s effect on cognitive function among centenarians. Garatachea et al. (2015) reported that carriage of the $\epsilon 4$ allele was negatively associated with the likelihood of reaching 100+ years old. Thus, the survival effect for individuals with the $\epsilon 4$ allele might hamper the evaluation of the effect of the *APOE* on cognitive function among centenarians. Using larger data from 904 participants aged 90 and over, Corrada et al. (2013) showed that the *APOE* $\epsilon 4$ was significantly associated with dementia prevalence among them adjusting for age and gender but was not related to incident dementia and mortality. Thus, large sample data must be collected to examine whether being an *APOE* $\epsilon 4$ allele carrier would be the risk for cognitive impairment among centenarians.

Also, there might be other factors that modified the effect of the *APOE* $\epsilon 4$ on cognitive function in late life. The role of gene–environment interactions for cognitive function in older adults has gained interest (Zeng et al. 2011). Educational attainment has been recognized as one of representative environmental factors that influences cognitive function in late life (Evans et al. 1993; White et al. 1994). As it is indicated the association between educational attainment and intelligence, the heritability of educational attainment has been shown around 20 % by genome-wide association studies (Rietveld, Medland, Derringer, et al., 2013); however, educational attainment is strongly influenced by environmental factors.

Wang et al. (2012) reported the modifying effect of education on the association between the *APOE* $\epsilon 4$ and dementia among 3436 participants aged 65 and over. The finding suggested that higher education during childhood might work to protect the negative effect of the $\epsilon 4$ allele on dementia in late life. As one possible mechanism, they mentioned the cognitive reserve hypothesis, which proposed highly intellectual environments, such as education and other life experiences might allow people to cope better with the brain

pathology than others (Stern 2009). In some centenarian studies, positive associations of higher education with cognitive function were observed (Kliegel et al. 2004; Li et al. 2010). Considering early-life education is needed to clarify the effect of *APOE* $\epsilon 4$ on cognitive function even in very late life.

The interaction effect of *APOE* $\epsilon 4$ and education would be contingent upon gender because men centenarian showed higher level in both cognitive function and educational attainment in comparison to women centenarian as reported from Tokyo Centenarian Study (Gondo et al. 2006). For that proposition, we examine the effects of the *APOE* $\epsilon 4$, education, and their interactions on cognitive function among centenarians, using a large sample of Japanese centenarian data. In addition, we test whether the $\epsilon 4$ allele's effect on cognitive function by education could depend on gender. First, we use educational attainment as it is and coded into three levels according to school enrollment (analysis 1). Second, to make clear the effect of education, we coded education into two levels. We classified secondary school attainment into high level for men and into low level for women (analysis 2). This coding was adopted to consider the social circumstances. In the early 1900s in Japan, higher educational attainment in women had been not accepted by the conservative social circumstances.

Methods

Study sample

Participants were derived from two centenarian cohorts: the Tokyo Centenarian Study (TCS; $n = 244$, aged 100 years and older) and the Japanese Semi-supercentenarians Study (JSS; $n = 208$, mainly aged 105 years and older). We performed the statistical analyses in a total of 452 (74 men and 378 women) participants for whom all necessary information was collected (Fig. 1).

The TCS ($n = 244$, aged 100 years and older) was conducted between July 2000 and May 2002 (Gondo et al. 2006). We randomly selected centenarians from the residential list of the 23 wards of metropolitan Tokyo and sent a mail inviting 1741 people to participate, of whom 1194 responded. Of the 304 participants in the visit survey, 60 persons had missing data on cognitive

Fig. 1 Flowchart of the 452 centenarians in the study

performance, genotypes, and education, leaving 244 participants for the analyses.

The JSS ($n = 208$, mainly aged 105 years and older) was a nationwide longitudinal survey started in 2002 (Arai et al. 2014). We used the data from the first to third phases. In the first phase, participants were selected from a cohort of individuals aged ≥ 105 years in Japan. Among the participants that had been included in the 2002 version of the oldest-old list ($N = 846$), which is published every September by the Ministry of Health, Welfare, and Labor. Of the 190 who agreed to participate, 144 participated in the visit survey. In the second phase, because the oldest-old list was discontinued in 2002, we recruited new participants during 2003–2008 using the following ways: (a) recruiting participants in the TCS, (b) finding names in the Basic Resident Registers in the 23 wards of Tokyo, or (c) locating names when the names and part of addresses were published in a newspaper or other media. Of the 97 who agreed to participate, 77 participated

in the visit survey. In the third phase, we recruited another participants during 2008–2009 using two ways: (a) requesting that the 5907 nursing homes in the entire country, except Okinawa, or (b) locating names when the names and part of addresses were published in a newspaper or other media. Of the 78 who agreed to participate, 73 participated in the visit survey. Out of 294, 56 people were also included in the both centenarian studies' visit survey. Their data collected at the TCS were included in this study. Out of 238 participants only in the JSS visit survey, 30 persons had missing data on cognitive performance, genotypes, and education, including 208 participants for the current study.

For participation in any of the studies, written informed consent was obtained either from the participants or by proxy when individuals lacked the capacity to consent. TCS and JSS were approved by the Ethical Committee of the Keio University School of Medicine and Tokyo Metropolitan Institute of Gerontology.

APOE genotyping

In the TCS, *APOE* genotypes (rs429358 and rs7412) were determined by polymerase chain reaction (PCR)–restriction fragment length polymorphism (RFLP), as previously described (Hirose et al. 1997). In the JSS, total DNA was isolated from venous blood by the use of QIAamp DNA Blood Maxi Kit (QIAGEN, Hilden, Germany). Genotyping was performed by pre-designed TaqMan® SNP genotyping assays [IDs: C___3084793_20 for Cys112Arg (rs429358) and C___904973_10 for Arg158Cys (rs7412)] (Applied Biosystems, Foster City, CA, USA). All samples were run in a StepOnePlus™ Real-Time PCR System (Applied Biosystems). A total of 5 ml genotyping mixture contained 2.5 ml GTXpress™ master mix, 0.125 ml assay mix (40×), and 1.375 ml distilled water to mix with 1 ml genomic DNA (10 ng/ml) in each reaction. One or two negative controls were included on each plate. TaqMan® SNP Genotyping Assays for genotype calls were analyzed by using StepOne™ Software v2.1 (Applied Biosystems).

We used a dichotomous classification for participants as either $\epsilon 4$ allele carriers or noncarriers in this analysis; previous research examining the relationship between *APOE* and cognitive function suggested that the presence of either one or two *APOE* $\epsilon 4$ alleles could influence the risk of cognitive function in old age (Seeman et al. 2005; Tang et al. 1998). Among the visit survey participants, we successfully collected sufficient blood samples to analyze the *APOE* genotype. Because of disagreement or health issues, we were unable to collect blood samples from the rest of participants.

Education

First, participants were divided into three groups according to school enrollment (analysis 1): low level (people who did not enter school up to primary school), middle level (people who attended secondary school), and high level (people who attended high school and more). Second, we coded secondary school attainment as different levels according to gender (analysis 2). Participants who attended secondary school were included into high level for men and into low level for women.

Cognitive function

We administrated the Mini-Mental State Examination (MMSE) (Folstein et al. 1975) to assess cognitive

function on all visit survey participants at the locations where the centenarians resided at the time of the visit survey. In some cases, the participants could not complete the MMSE. We scored the participants who were “bedridden and unable to give a response” and “inability to follow instructions” as MMSE 0.

Statistical analyses

The chi-squared test was performed to compare the frequency distribution of *APOE* $\epsilon 4$ carriers between education and gender. Second, we conducted the Hayes PROCESS macro (model 3) for a moderated moderation analysis (Hayes 2013), which is better known as three-way interaction based on ordinary least squares regression model, because the interaction effects between the $\epsilon 4$ allele and education might depend on gender. The model included age as a potential confounder, the $\epsilon 4$ allele, education, and interactions (*APOE* $\epsilon 4$ by gender, education by gender, *APOE* $\epsilon 4$ by education, and *APOE* $\epsilon 4$ by education by gender). As for education, we examined the effect of education with three levels both in gender (analysis 1) and with a different coding according to gender (analysis 2). Statistical significance was set at $p < 0.05$, and two-sided tests were applied. All analyses were performed using IBM SPSS19.0-J. software (IBM, Tokyo, Japan).

Results 1

Table 1 lists the characteristics of the participants in this study. About 83.6 % were women. The age of the participants ranged from 100 to 115 years old, and the average age (SD) was 103.6 (3.2) years old. Approximately 15.9 % had a high educational level, and men had higher percentage of high education level than the women (40.5 and 11.1 %, respectively; $\chi^2 = 43.45$, $p < 0.001$). The *APOE* $\epsilon 4$ carrier was similarly distributed among the educational levels (8.4, 9.8, and 11.1 %, respectively, for the low, the middle, and the high educational level; $\chi^2 = 0.58$, $p = 0.75$) and gender (4.1 and 10.1 %, respectively, for men and women; $\chi^2 = 2.70$, $p = 0.10$).

In analysis 1, moderated moderation analysis was performed with the MMSE score as a dependent variable and the *APOE* $\epsilon 4$ allele, education, gender, and three interactions as independent variables. The result is shown in Table 2. The data showed that main effects of the carriage of the $\epsilon 4$ allele and education on the

Table 1 Characteristics of 452 participants with complete data for analysis

Characteristic	Gender				Total	
	Men		Women		N	%
	N	%	N	%		
No. of participants	74	16.4	378	83.6	452	100.0
Age group (years)						
100	31	41.9	112	29.6	143	31.6
101–102	15	20.3	49	13.0	64	14.2
103–104	7	9.5	27	7.1	34	7.5
105–106	10	13.5	91	24.1	101	22.3
107–109	9	12.2	90	23.8	99	21.9
110 ≤	2	2.7	9	2.4	11	2.4
Mean (SD)	102.5	(3.0)	103.8	(3.2)	103.6	(3.2)
<i>APOE</i> allele						
ε4 carrier	3	4.1	38	10.1	41	9.1
ε4 noncarrier	71	95.9	340	89.9	411	90.9
<i>APOE</i> genotype						
e2/e2	0	0.0	2	.5	2	.4
e2/e3	17	23.0	49	13.0	66	14.6
e3/e3	54	73.0	288	76.2	342	75.7
e4/e2	0	0.0	1	.3	1	.2
e4/e3	3	4.1	34	9.0	37	8.2
e4/e4	0	0.0	4	1.1	4	.9
Education						
Low education	40	54.1	258	68.3	298	65.9
Middle education	4	5.4	78	20.6	82	18.1
High education	30	40.5	42	11.1	72	15.9
MMSE score						
≥21	27	36.5	44	11.6	71	15.7
11–20	24	32.4	103	27.2	127	28.1
6–10	7	9.5	71	18.8	78	17.3
0–5	16	21.6	160	42.3	176	38.9
Mean (SD)	15.2	(9.2)	8.6	(8.4)	9.7	(8.9)

MMSE score were significant ($B = -4.27$, $SE = 1.37$, $t = -3.12$, $p < 0.01$ and $B = 1.21$, $SE = 0.52$, $t = 2.35$, $p < 0.05$), indicating higher MMSE score in the *APOE* ε4 noncarriers and in the higher education. In addition, there was a statistically significant three-way interaction between the *APOE* ε4 allele, education, and gender ($B = 12.76$, $SE = 5.63$, $t = 2.27$, $p < 0.05$). The conditional effect of the *APOE* ε4 by the education interaction was marginally significant only among men ($p < 0.05$).

Analysis 2 also showed that main effects of the *APOE* ε4 allele and education and three-way interaction

between the *APOE* ε4 allele, education, and gender were significant (Table 3). The conditional effects of the *APOE* ε4 by the education interaction were significant in both gender. For men, there was a significant simple effect of the ε4 allele only in the high educational group, indicating that a ε4 carrier had a lower MMSE score than noncarrier. For women, a ε4 carrier showed a lower MMSE score than noncarrier in the lower educational group; on the other hand, the MMSE score for those with high education levels showed no difference between the ε4 carriers and noncarriers.

Table 2 Moderated moderation analysis with the MMSE score as a dependent variable and age, the *APOE* $\epsilon 4$ allele, education, and three interactions as independent variables (Analysis 1)

	<i>B</i>	<i>SE</i>	<i>t</i> value	<i>p</i> value	Lower LCI	Upper LCI
Constant	123.56	11.83	10.44	0.00	100.30	146.82
Age	−1.10	0.11	−9.63	0.00	−1.33	−0.88
APOE	−4.27	1.37	−3.12	0.00	−6.96	−1.58
Education	1.21	0.52	2.35	0.02	0.19	2.23
Gender	−3.78	1.06	−3.56	0.00	−5.86	−1.69
APOE $\times$ education	0.29	1.65	0.17	0.86	−2.95	3.53
APOE $\times$ gender	5.30	5.33	0.99	0.32	−5.18	15.78
Education $\times$ gender	−0.87	1.12	−0.78	0.044	−3.08	1.34
APOE $\times$ education $\times$ gender	12.76	5.63	2.27	0.02	1.69	23.83
Conditional effect of APOE $\times$ education at values of gender						
Gender	Effect	<i>SE</i>	<i>t</i> value	<i>p</i> value	Lower LCI	Upper LCI
Man	−10.38	5.38	−1.93	0.05	−20.96	0.19
Woman	2.38	1.67	1.43	0.15	−0.90	5.65

Note: The variables, APOE, gender, and education were mean-centered prior to analysis. Gender: man = 1, woman = 2; APOE $\epsilon 4$ allele: the $\epsilon 4$ noncarriers = 0, the $\epsilon 4$ carriers = 1; education: low = 1, middle = 2, high = 3

Figure 2 illustrates the graphical illustrations of the estimated MMSE scores shown separately for gender and the educational groups in those with and without the $\epsilon 4$ allele.

Table 3 Moderated moderation analysis with the MMSE score as a dependent variable and age, the *APOE* $\epsilon 4$ allele, education, and three interactions as independent variables (Analysis 2)

		<i>B</i>	<i>SE</i>	<i>t</i> value	<i>p</i> value	Lower LCI	Upper LCI
Constant		127.09	11.62	10.94	0.00	104.25	149.93
Age		−1.13	0.11	−10.11	0.00	−1.36	−0.91
APOE		−3.55	1.50	−2.37	0.02	−6.50	−0.61
Education		1.68	1.10	1.53	0.13	−0.48	3.84
Gender		−3.71	1.17	−3.17	0.00	−6.00	−1.41
APOE × education		3.10	3.24	0.96	0.34	−3.27	9.46
APOE × gender		1.30	6.52	0.20	0.84	−11.51	14.11
Education × gender		−1.97	2.22	−0.89	0.38	−6.32	2.39
APOE × education × gender		27.80	9.96	2.79	0.01	8.24	47.37
Conditional effect of APOE x education at values of gender							
Gender		Effect	<i>SE</i>	<i>t</i> value	<i>p</i> value	Lower LCI	Upper LCI
Man		−20.15	9.35	−2.15	0.03	−38.54	−1.77
Woman		7.65	3.41	2.24	0.03	0.94	14.35
Conditional effect of APOE on the MMSE at values of gender x education							
Gender	Education	Effect	<i>SE</i>	<i>t</i> value	<i>p</i> value	Lower LCI	Upper LCI
Man	Low	−1.26	7.60	−0.17	0.87	−16.19	13.68
Man	High	−21.41	5.47	−3.91	0.00	−32.16	−10.66
Woman	Low	−4.63	1.41	−3.27	0.00	−7.40	−1.85
Woman	High	3.02	3.11	0.97	0.33	−3.08	9.12

The variables, APOE, gender, and education were mean-centered prior to analysis. Gender: man = 1, woman = 2; APOE $\epsilon 4$ allele: the $\epsilon 4$ noncarriers = 0, the $\epsilon 4$ carriers = 1; education: low = 1, high = 2

Fig. 2 Estimated score of the MMSE as a category of the APOE $\epsilon 4$ carrier and education in men and women. Estimates were based on setting covariates to their sample means. Note Fig. 1 displays estimated MMSE score according to the result from the moderated moderation analysis (analysis 2). There were 33 participants (1 man and 32 women) who were APOE $\epsilon 4$ carrier in the low educational group (*dagger*). There were 9 participants (2 man and 7 women) who were APOE $\epsilon 4$ carrier in the high educational group (*double dagger*)

Discussion

Using a large centenarian data, we examined the effect of the APOE $\epsilon 4$, education, and their interactions on cognitive function. The effects of the APOE $\epsilon 4$ and education were significant even among centenarians as same as among young-old adults. Further, three-way interaction (the APOE $\epsilon 4$, education, and gender) was statistically significant. The results indicated that the effects of both APOE and education were consistent throughout long life, even for the individuals who lived 100 years. In addition, our results suggest that the interaction between the APOE $\epsilon 4$ allele and education on cognition is dependent on gender in this cohort.

When we coded education based on the formal educational levels, there was a significant effect of education on cognitive function (analysis 1). It suggests that higher education may contribute to the development of brain function at a young age and retard cognitive impairment in the oldest-old adults (Deary et al. 2007). However, there were gender differences in interaction between APOE and education. When we considered a periodical background of educational attainment, gender differences in the association between gene and education were clearly shown (analysis 2). The results showed that the $\epsilon 4$ carrier men had a lower MMSE score than noncarrier in the higher educational group. On the other hand, the MMSE score for women with high education levels showed no difference between the $\epsilon 4$ carriers and noncarriers. Therefore, the results indicated

that education might buffer the effect of the $\epsilon 4$ allele on cognitive function only among women centenarians.

With regard to the gender differences in the interaction between gene and education, we can speculate two possible pathways in relation to gender differences in their life courses. One is background to get higher educational attainment. Second are influences of educational attainments during adulthood. In the early twentieth century in Japan, men had gotten higher educational attainment than women. Regardless of intellectual abilities during childhood, women could not attend secondary or high school. Therefore, women centenarians who were the higher educated did not have higher MMSE scores as same as men. This dissociation may suggest that life context after formal education in men are more diversified in centenarians, and higher educational attainment provides more opportunities to live in an enriched and advantageous environment. On the other hand, we assume that life context after formal education in women was not diversified compared to men and depending on spouse socioeconomic status. As a result, the predicted power of education on cognitive function may be lower in women than men who grew up during this era. Life course differences between men and women indicate that it is needed to evaluate gene environment, such as their early-life intellectual abilities, education, occupation of self and spouse, and activities.

Another pathway is the status of the mid-life environment, which also has an influence on cognitive function in later life. There has been evidence to support that

an enriched environment such as an active lifestyle in middle age may directly or indirectly act to prevent or slow cognitive decline in later life (Bosma et al. 2003). Therefore, the protective effect of education in advanced age may not be as strong as expected.

In our data, there were only three men with the $\epsilon 4$ allele, and only one man with higher education was an *APOE* $\epsilon 4$ carrier; his MMSE score was 0. One explanation may be that men are more vulnerable to the *APOE* $\epsilon 4$ allele survival effect than women. The frequency distribution of *APOE* $\epsilon 4$ carriers between gender was not significantly different, but the *P* value was 0.10 in the chi-squared test. Future study using a much larger sample of men will examine whether our findings are replicated.

In previous studies on centenarians, effects of the *APOE* $\epsilon 4$ allele on cognitive function have been inconsistent (Asada et al. 1996; Choi et al. 2003; Sobel et al. 1995). These inconsistent findings could be attributed to common characteristics of centenarian studies: small sample size, skewed distribution of *APOE* genotype, and lesser attention of researchers with regard to the effect of life course environment on cognitive function in centenarian study (Hofer and Alwin 2008). First, the number of participants which analyzed in the previous centenarian studies were small ($N = 33, 103, \text{ and } 179$, respectively, Asada et al. 1996; Choi et al. 2003; Sobel et al. 1995). Second, the *APOE* gene has been associated with longevity; centenarians tend not to have the *APOE* $\epsilon 4$ allele (Ewbank 2002; Farrer et al. 1997). The selective survival effect for *APOE* $\epsilon 4$ -negative individuals makes it difficult to evaluate the effect of *APOE* on outcomes in very late life population. Third, little attempt has been made to consider the protective effect of education on cognitive function in very old age, although studies have consistently shown a relationship between education and cognitive function in younger-old adults. This distribution of number of participants who have the *APOE* $\epsilon 4$ allele was skewed as shown in this study; however, all three problems were resolved by using a larger number of participants.

The current study reported the effects of *APOE* and education and the interaction between *APOE*, education, and gender; however, there were limitations to this research. Some studies that examined the interaction between *APOE* and education for cognitive decline found that education could have limited protective power in young-old age. Using a 7-year follow-up period data, Seeman et al. (2005) reported that the presence of

the $\epsilon 4$ allele may reduce the effect of education. Moreover, van Gerven et al. (2012), who followed their study's participants over a period of 12 years, found that older, highly educated carriers of the *APOE* $\epsilon 4$ allele demonstrated a more pronounced decline than younger, lower educated carriers, and noncarriers. Our findings indicated that there was a protective effect of education on cognitive function at the end of life. We could not follow up and examine how cognitive function may change in individuals. Further studies with *APOE*, education, socioeconomic status, and the mid-life environment in the oldest-old cohorts are warranted for a better understanding of cognitive aging in the oldest-old and centenarians.

In conclusion, this study examined the interactive effects of *APOE* and education on cognitive function among centenarians and suggested that the $\epsilon 4$ allele is a life-long risk factor for cognitive impairment. High educational attainment can protect the negative effects of this gene and may create a greater reserve capacity throughout the life span. However, the interaction between *APOE* and education might depend on gender in this cohort. These findings also suggest that researchers should carefully examine the effects of life environmental situations from early age to late life in parallel to understand the environmental interaction of genes on cognitive function even in the centenarians.

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Compliance with ethical standards For participation in any of the studies, written informed consent was obtained either from the participants or by proxy when individuals lacked the capacity to consent. TCS and JSS were approved by the Ethical Committee of the Keio University School of Medicine and Tokyo Metropolitan Institute of Gerontology.

References

- Arai Y, Inagaki H, Takayama M, et al. (2014) Physical independence and mortality at the extreme limit of life span: supercentenarians study in Japan. *J Gerontol A Biol Sci Med Sci* 69(4):486–494
- Asada T, Yamagata Z, Kinoshita T, Kinoshita A, Kariya T, Asaka A, Kakuma T (1996) Prevalence of dementia and distribution of ApoE alleles in Japanese centenarians: an almost-complete survey in Yamanashi Prefecture, Japan. *J Am Geriatr Soc* 44(2):151–155
- Bosma H, van Boxtel MPJ, Ponds RWHM, Houx PJH, Jolles J (2003) Education and age-related cognitive decline: the contribution of mental workload. *Educ Gerontol* 29(2):165–173
- Choi Y-H, Kim J-H, Kim DK, et al. (2003) Distributions of ACE and APOE polymorphisms and their relations with dementia status in Korean centenarians. *J Gerontol Ser A Biol Med Sci* 58(3):227–231
- Corrada MM, Paganini-Hill A, Berlau DJ, Kawas CH (2013) Apolipoprotein E genotype, dementia, and mortality in the oldest old: the 90+ Study. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 9(1):12–18
- Deary IJ, Gow AJ, Taylor MD, et al. (2007) The Lothian Birth Cohort 1936: a study to examine influences on cognitive ageing from age 11 to age 70 and beyond. *BMC Geriatr* 7:28
- Dik MG, Jonker C, Comijs HC, Bouter LM, Twisk JW, van Kamp GJ, Deeg DJ (2001) Memory complaints and APOE-epsilon4 accelerate cognitive decline in cognitively normal elderly. *Neurology* 57(12):2217–2222
- Evans DA, Beckett LA, Albert MS, Hebert LE, Scherr PA, Funkenstein HH, Taylor JO (1993) Level of education and change in cognitive function in a community population of older persons. *Ann Epidemiol* 3(1):71–77
- Ewbank DC (2002) Mortality differences by APOE genotype estimated from demographic synthesis. *Genet Epidemiol* 22(2):146–155
- Farrer LA, Cupples L, Haines J, et al. (1997) Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. *JAMA: The Journal of the American Medical Association* 278(16):1349–1356
- Folstein MF, Folstein SE, McHugh PR (1975) “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12(3):189–198
- Garatachea N, Marín PJ, Santos-Lozano A, Sanchis-Gomar F, Emanuele E, Lucia A (2015) The ApoE gene is related with exceptional longevity: a systematic review and meta-analysis. *Rejuvenation Res* 18(1):3–13
- Giubilei F, Medda E, Fagnani C, et al. (2008) Heritability of neurocognitive functioning in the elderly: evidence from an Italian twin study. *Age Ageing* 37(6):640–646
- Gondo Y, Hirose N, Arai Y, et al. (2006) Functional status of centenarians in Tokyo, Japan: developing better phenotypes of exceptional longevity. *J Gerontol A Biol Sci Med Sci* 61(3):305–310
- Hayes A (2013) Introduction to mediation, moderation, and conditional process analysis: a regression-based approach. Guilford Press, New York, NY
- Hirose N, Homma S, Arai Y, et al. (1997) [Tokyo Centenarian Study. 4. Apolipoprotein E phenotype in Japanese centenarians living in the Tokyo Metropolitan area]. *Nihon Ronen Igakkai Zasshi Japanese Journal of Geriatrics* 34(4):267–272
- Hofer SM, Alwin DF (2008) Handbook of cognitive aging: interdisciplinary perspectives. Sage Publications, Thousand Oaks, CA
- Kliegel M, Zimprich D, Rott C (2004) Life-long intellectual activities mediate the predictive effect of early education on cognitive impairment in centenarians: a retrospective study. *Aging Ment Health* 8(5):430–437
- Li J, Dong B-R, Lin P, Zhang J, Liu G-J (2010) Association of cognitive function with serum uric acid level among Chinese nonagenarians and centenarians. *Exp Gerontol* 45(5):331–335
- Mahley R (1988) Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science* 240(4852):622–630
- Mahley R, Rall S (2000) Apolipoprotein E: far more than a lipid transport protein. *Annu Rev Genomics Hum Genet* 1:507–537
- Raber J, Huang Y, Ashford JW (2004) ApoE genotype accounts for the vast majority of AD risk and AD pathology. *Neurobiol Aging* 25(5):641–650
- Seeman TE, Huang M-H, Bretsky P, Crimmins E, Launer L, Guralnik JM (2005) Education and APOE-epsilon4 in longitudinal cognitive decline: MacArthur Studies of Successful Aging. *J Gerontol Ser B Psychol Sci Soc Sci* 60(2):74–83
- Small BJ, Rosnick C, Fratiglioni L, Backman L (2004) Apolipoprotein E and cognitive performance: a meta-analysis. *Psychol Aging* 19(4):592–600
- Sobel E, Louhija J, Sulkava R, et al. (1995) Lack of association of apolipoprotein E allele epsilon 4 with late-onset Alzheimer's disease among Finnish centenarians. *Neurology* 45(5):903–907
- Stern Y (2009) Cognitive reserve. *Neuropsychologia* 47(10):2015–2028
- Tang MX, Stern Y, Marder K, et al. (1998) The APOE-epsilon4 allele and the risk of Alzheimer disease among African Americans, whites, and Hispanics. *JAMA: The Journal of the American Medical Association* 279(10):751–755
- van Gerven PWM, van Boxtel MPJ, Aulsems EEB, Bekers O, Jolles J (2012) Do apolipoprotein E genotype and educational attainment predict the rate of cognitive decline in normal aging? A 12-year follow-up of the Maastricht Aging Study. *Neuropsychology* 26(4):459–472
- Wang H-X, Gustafson DR, Kivipelto M, Pedersen NL, Skoog I, Windblad B, Fratiglioni L (2012) Education halves the risk of dementia due to apolipoprotein epsilon4 allele: a collaborative study from the Swedish brain power initiative. *Neurobiol Aging* 33(5):1007.e1–1007.e7
- White L, Katzman R, Losonczy K, et al. (1994) Association of education with incidence of cognitive impairment in three established populations for epidemiologic studies of the elderly. *J Clin Epidemiol* 47(4):363–374
- Zeng Y, Hughes CL, Lewis MA, Li J, Zhang F (2011) Interactions between life stress factors and carrying the APOE4 allele adversely impact self-reported health in old adults. *J Gerontol A Biol Sci Med Sci* 66(10):1054–1061