**Research Article** 



# Exploring APOE Epsilon4 Genotype to Predict MCI-to-AD Dementia: A Meta- Analysis

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#### ABSTRACT

**Background:** APOE4 have been considered as the risk of AD, but the predict value of MCI progressing to AD was not clear.

**Objective:** The aim of the current study was to investigate the predictive-value of APOE4+ in the development of Mild Cognitive Impairment (MCI) to Alzheimer's Disease (AD) using a meta-analysis.

**Methods:** At PubMed, Elsevier Science Direct, Scihub and Google Scholar we searched all the previous cohort studies on APOE4+ genotype associated with the risk of MCI-to-AD dementia, published before January 1, 2019. Stata Meta-DiSc (version 1.4) software was used to pool the APOE4+ prognosis data to examine the sensitivity, specificity and the summary receiver operating characteristic curve (SROC) in predicting the risk MCI-to-AD dementia; Stata software, to calculate the relative risk (RR) and 95% CIs.

**Results:** For the meta-analysis were involved 43 previously reported studies, where it was found that in MCI people aged  $\geq$ 70, who had progressed to AD dementia within 5 years, the APOE4+ predictive sensitivity was 0.71; the specificity, 0.71; and AUC, 0.78. Moreover, the results showed that RR was 1.49 and 1.56, respectively, for MCI people in general and for MCI people aged  $\geq$ 70 and with the risk of APOE4+-to-AD. Particularly, the RR was 2.24 for the individuals aged  $\geq$ 70 and with APOE4+ who progressed to AD dementia within 5 years.

**Conclusion:** The findings strongly suggested that it could take less than 5 years for MCI people aged  $\geq$ 70 and with the gene of APOE4 to progress to AD dementia.

# Introduction

Alzheimer's Disease (AD) is a neurodegenerative disease which has high morbidity and mortality. The world Alzheimer's report in 2018 showed that globally there were about 500 million patients afflicted with AD, with its mortality being approximately 4.5%, leading to one of the top five causes of death in the world [1,2]. Mild Cognitive Impairment (MCI) is a significant cognitive deficit, but not qualified as a dementia reference, while in older patients MCI progresses to dementia at a rate of 60-100% in 5-10 years [3,4]. Furthermore, a meta-analysis found that 5%-15% of amnestic

MCI (aMCI) patients aged over 65 developed AD dementia every year; however, a part of MCI kept stable or even reverted to normal [5]. Therefore, it is important that we have a differentiation of the MCI which has a tendency to progress to AD, which is beneficial to clinical prevention and therapy. Cheng et al discovered that the cortical thinning in the temporal region reflected a cognitive change in the MCI patients, which could be of a useful prediction of MCI progressing to AD dementia [6]. A review provided a critical examination of MCI's clinical concept, stressing an increased focus on the impact of Cerebrovascular Disease (CVD) and CVD risk during the prodromal period of AD dementia [7].

Many risk factors have been reported to be associated with AD such as A $\beta$  and tau [8,9]. The other investigations have found  $\varepsilon$ 4 allele of the apolipoprotein E gene (APOE $\varepsilon$ 4+) as a risk genetic factor for AD dementia and MCI [10-12]. However, it was found to be a significant risk factor for AD dementia rather than for MCI [13]. A previously reported investigation on a Chinese MCI population discovered that both aMCI patients and normal ageing people who carried APOE  $\varepsilon$ 4+ had a high risk of MCI progressing to AD dementia, the hazard ratio 2.0 and 5.3, respectively [14]; the differentiation indicated that the risk of progressing to AD dementia was lower in MCI with APOE ɛ4+ than in normal ageing with APOE ε4+. Given the relationship between APOE ε4+ and MCI/ AD, the predicting value of APOE £4+ progressing to MCI or to AD dementia has become one of research focuses on the field recently [15,16]. But the contradictory results still exist based on different experiments. Elias-Sonnenschein and Li conducted a meta-analysis so as to assess the different ORs in different experiments on MCI patients with APOE £4+ progressing to AD dementia [17,18], which pooled all the reports before 2008 and 2014, respectively. The review's outcomes turned out to be that that those with MCI and APOEɛ4+ presented a high risk for AD dementia progression.

Oveisgharan S et al found the evidence that APOE  $\varepsilon 2\varepsilon 4$  genotype in older adults was associated with MCI risk, as a greater burden of AD pathology [19]. On the contrary, APOE  $\varepsilon 4+$  was reported to be incapable of predicting the conversion MCI to AD dementia without using biomarkers [20], and APOE  $\varepsilon 4+$ , to be not associated with the development of MCI and AD [21]. The diagnostic value of APOE  $\varepsilon 4+$  for MCI-to-AD dementia still remains unknown in terms of sensitivity and specificity. Thus, it is necessary that we reassess the diagnostic-value of the APOE  $\varepsilon 4+$  for MCI-to-AD. The aim of the current meta-analysis was to reassess the diagnostic and prognostic value of APOE  $\varepsilon 4+$  for MCI-to-AD dementia in different subgroups.

## Methods

#### Search Strategy and Selection Criteria

The relevant literature ranging from January 1, 1987 to May 1, 2019 was systematically pursued at the PubMed, Elsevier Science Direct, Scihub and Google Scholar, with the searching key words as Apolipoprotein E/APOE, mild cognitive impairment/MCI,

Alzheimer's disease/AD/dementia. Some papers were traced via a reference link in the relevant literature.

#### **Inclusion and Exclusion Criteria**

The studies and investigations on the association of APOE  $\epsilon$ 4 allele with MCI progressing to AD dementia were included, the criteria of which were as follows:

- a) Original studies
- b) Reported in English

c) Petersen and co- workers criteria used for MCI [22], NINCDS-ADRDA criteria for AD [23]

d) Complete description of the MCI group without AD progress and of the MCI group with

- e) APOE ε4 allele recorded
- f) Case-control study or cohort study in nature

g) Full text available, or the requisite information from the authors.

The studies and investigations were excluded if the study sample included:

- a) Abstract, literature review, case report, seminar
- b) Other languages except English
- c) Criteria of MCI and AD not explicitly described

d) Not clearly described MCI group with and without MCI-to-AD dementia

- e) Recorded APOE ɛ4 allele not well founded
- f) Not a case-control study or a cohort study
- g) Full text not available.

#### Literature Quality Assessment

Each study was read by two coauthors (Juan Yang and Xiaohui Zhao), who would have a discussion over a contentious point, if any, before reaching a consensus. Study quality was assessed with the Quality Assessment of Diagnostic Accuracy Studies 2(QUADAS-2) for studies [15].

## **Data Extraction**

APOE with and withoutɛ4 allele was recorded as APOE4+ and APOE4-, respectively. NINCDS-ADRDA criteria for AD were considered as the goldenstandard, and APOEɛ4, as the diagnostic maker. The number of True Positive (TP), True Negative (TN), False Positive (FP) and False Negative (FN) were extracted from all the reports. Otherwise, tabulated were the authors, publication date, country of the study population, age, gender, MCI subtype, years of follow-up, baseline score of MMSE and years of education.

#### **Statistical Analysis**

Meta-DiSc (version 1.4, Unit of Clinical Biostatistics team of the Ramón Cajal Hospital in Madrid, Spain) software was used to analyze the sensitivity and specificity and the summary receiver operating characteristic curve (SROC). Sensitivity (TP rate) referred to the proportion of MCI to AD dementia, correctly identified as APOE4+; specificity (1-FP rate), to the proportion MCI to AD dementia, correctly identified as APOE4-. Heterogeneity was assessed using I<sup>2</sup> and Tau<sup>2</sup>; publication bias was analyzed and represented by a funnel plot, and funnel plot symmetry was assessed with Egger's test [24]. Stata12.0 software (Stata Corp LP, College Station, TX, USA) was used to pool the relative risk (RR), and the RR and 95%CIs, to summarize the risk of MCI-to-AD with APOE4+. Statistical significance was defined as P < 0.05.

#### Results

#### **Search Results**

A total of 9038 studies were indexed in the primary screen and search, 1972 of which were duplicates. It was found from the screening that 7028 articles did not meet the relation of APOE  $\epsilon$ 4 allele to MCI-to-AD dementia to be excluded, and that 10 articles failed to meet our including criteria to be excluded. Consequently, a total of 43 studies [14,25-61] were enrolled for the current metaanalysis. As indicated in Figure 1, a full description was made of the search strategy.



Figure 1: Flow diagram of study selection.

#### **Study Characteristics**

As indicated in Table 1, a list was made of the characteristics of 38 articles included for the meta-analysis. A total of 5,040 subjects with MCI were characterized by a period of 1-8 year clinical follow-up observation, at the end of which, the number of TP, FP, FN and TN were 1,039, 1,221, 728 and 2,052, respectively. The mean age of MCI-AD dementia and MCI-MCI was 72.69±8.12 and 70.0±7.31 years, respectively, the females of MCI-AD dementia

and MCI-MCI accounting for 51.11% and 54.36%, respectively. The mean educational years of MCI-AD dementia and MCI-MCI were 11.61±3.47 and 11.31±3.36, respectively. The mean baseline-MMSE-score of MCI-AD dementia and MCI-MCI was 26.12±1.94 and 27.28±1.94, respectively. Furthermore, MCI-classification in all studies was classified as aMCI and mix-MCI (not defined as aMCI). Three geographic regions were defined: China (including Taiwan) pertained to Asia; Netherlands/America, to North America; and Canada/Sweden/Italy/Germany, to Europe.

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						MCI-AD dementia	MCI-MCI	MCI-AD dementia	MCI-MCI	MCI-AD (	(gender)
Author	Year	TP	FP	FN	TN	APOE4+	APOE4-	APOE4+	APOE4-	Female	Male
Tierney	1996	16	26	13	52	16	13	26	52	_	_
Korf	2004	22	15	15	23	22	15	15	23	25	12
Devanand	2005	32	20	5	82	32	5	20	82	21	14
Drzezga	2005	9	8	3	10	9	3	8	10	6	6

Randall Griffith	2005	5	12	5	22	5	5	12	22	10	3
Stoub	2005	7	8	7	32	7	7	8	32	10	4
Dong Young Lee	2006	9	11	5	44	9	5	11	44	9	5
Bouwman	2006	23	11	10	15	23	10	11	15	11	15
Herukka	2006	26	15	7	30	26	7	15	30	20	13
Tapiola	2006	8	21	5	26	8	5	21	26	8	5
Barabash	2007	29	9	31	18	29	31	9	18	40	22
Forsberg	2007	6	8	1	6	6	1	8	6	6	1
Luca Rozzini	2007	24	27	16	52	24	16	27	52	29	11
Anna Caroli	2007	5	6	4	8	5	4	6	8	4	5
Ewers	2007	6	4	2	5	6	2	4	5	5	3
Ewers	2007	12	12	6	7	12	6	12	7	11	8
Ewers	2007	5	1	0	4	5	0	1	4	7	6
Ewers	2007	2	2	1	6	2	1	2	6	1	2
Fleisher	2007	161	143	51	184	161	51	143	184	99	113
Howard H Feldman	2007	29	86	20	113	29	20	86	113	65	44
Gavrilova	2008	4	6	1	2	4	1	6	2	_	_
Kester	2011	27	30	31	12	27	31	30	12	21	21
Davatzikos	2011	42	83	27	87	42	27	83	87	30	39
Jieping Ye	2012	94	74	48	103	94	48	74	103	_	_
Vosa	2012	29	42	19	63	29	19	42	63	24	24
Prestia	2015	15	21	14	23	15	14	21	23	18	11
Spampinato	2016	83	47	47	68	83	38	47	68	46	75
Lei Zheng	2016	46	33	30	55	46	30	33	55	44	32
Falahati	2017	46	33	24	42	46	24	33	42	43	27
Hansson O	2006	43	28	14	28	43	14	28	28	16	41
Spulber	2012	6	16	16	28	6	16	16	28	8	4
Liu	2007	35	76	7	8	35	7	76	8	14	28
Gabryelewicz	2007	9	17	14	65	9	14	17	65	14	9
Erten-Lyons	2006	4	3	19	11	4	19	3	11	19	4
Wang	2005	6	8	13	31	6	13	8	31	7	12
Hsiung	2004	22	24	48	90	22	48	24	90	—	_
Amieva	2003	11	27	18	34	11	18	27	34	7	22
ALBERT	2001	9	36	14	87	9	14	36	87	_	_
Varatharajah	2019	6	3	33	93	6	33	3	93	19	20
Meester (A)	2018	27	92	36	199	27	36	92	199	26	37
Meester (C)	2018	32	56	51	130	32	51	56	130	34	49
Meester (B)	2018	2	10	3	36	2	3	10	36	4	1
Mosconi	2004	5	11	3	18	5	3	11	18	5	3

		MCI-MCI	(gender)	MCI-AD dementia(age)			M	ICI-MCI(age	e)	MCI-AD(year of education)			
author	year	Female	Male	n1	mean1	<b>S1</b>	n2	mean2	S2	n1	mean1	<b>S1</b>	
Tierney	1996	-	-	29	74.4	7.1	78	71.5	7.8	29	13.3	3	
Korf	2004	20	18	37	65.2	7.4	38	60.6	10.3	37	9.9	2.7	
Devanand	2005	56	46	35	73	7.2	101	65	10	35	14	4.7	
Drzezga	2005	10	8	12	74.7	4.7	18	67.6	8.2	12	12.4	3.7	

Randall Griffith	2005	26	10	10	70.15	6.4	34	67.86	9.25	10	13.54	1.94
Stoub	2005	28	16	14	81	6	44	80	6	14	18	3
Dong Young Lee	2006	35	20	14	71.1	6.7	55	73.6	6	14	8.5	4.5
Bouwman	2006	19	14	33	70	8	26	69	8	_	_	-
Herukka	2006	26	20	33	71.67	6.71	45	69.46	8.14	-	_	-
Tapiola	2006	33	14	13	72.1	4.2	47	72.9	4.2	13	6.6	1.9
Barabash	2007	19	8	60	77	74	27	74		-	_	-
Forsberg	2007	7	7	7	63.4	7.9	14	62.6	8.4	7	13	3.7
Luca Rozzini	2007	45	34	40	73.5	8.5	79	69.2	7	40	7.7	3.7
Anna Caroli	2007	6	8	9	69	3	14	71	8	9	11.4	5.7
Ewers	2007	1	8	7	73.8	5.2	9	66	10.2	-	_	-
Ewers	2007	8	11	19	75.2	6.8	19	69.1	8.2	-	_	-
Ewers	2007	4	5	13	71.7	7	9	66.8	5.3	-	_	-
Ewers	2007	4	4	3	69.7	3.5	8	73.73	6.4	-	_	-
Fleisher	2007	132	195	212	74.87	6.64	327	71.52	7.41	212	14.47	3.1
Howard H Feldman	2007	197	204	109	73.6	6.6	401	69	7.7	109	10.6	4.1
Gavrilova	2008	-	_	5	72	6.2	31	67.7	7.1	-	-	-
Kester	2011	20	38	42	69	7	58	67	9	42	5	1
Davatzikos	2011	67	103	69	76.9	6.88	170	74.5	7.35	_	_	-
Jieping Ye	2012	_	_	142	74.49	6.94	177	74.9	7.39	142	15.77	2.9
Vosa	2012	43	62	48	70.4	7.2	105	68.8	7.3	48	11.2	3
Prestia	2015	23	21	29	67.6	6.8	44	65.3	6.9	29	11.59	3.29
Spampinato	2016	40	75	121	75.9	6.2	115	75.4	6.8	-	_	_
Lei Zheng	2016	42	46	75	68.3	4.2	86	72.6	4.6	-	-	-
Falahati	2017	60	15	70	74.3	6.9	75	74.5	7.4	70	15.8	3.2
Hansson O	2006	30	26	57	75		56	67	-	-	-	-
Spulber	2012	27	21	12	73.03	6.9	48	73.03	5.04	12	6.5	3.06
Liu	2007	31	51	42	77.1	5.5	82	73.5	5.4	42	11.1	5
Gabryelewicz	2007	57	25	23	71.7	8.2	82	68.7	7.2	—	_	_
Erten-Lyons	2006	7	7	23	87.69	5.21	17	85.72	6.84	23	13	3.3
Wang	2005	8	31	19	77.6	4.6	39	75.6	3.6	19	11.7	5.7
Hsiung	2004	_	_	_	—	-	_	-	-	-	_	-
Amieva	2003	33	28	29	73.3	5.8	61	68.7	7.9	-	-	-
ALBERT	2001	-	_	_	—	-	_	-	-	-	-	-
Varatharajah	2019	48	48	_	—	-	_	-	-	-	-	-
Meester(A)	2018	138	153	63	69	7.1	291	61.2	9.6	63	14	44
Meester(C)	2018	71	115	83	68	8.4	186	64.5	7.8	83	13.3	3.3
Meester(B)	2018	34	12	5	70.2	8.3	46	64.9	6.4	5	11.6	4.3
Mosconi	2004	15	14	8	71	5	29	66	8	8	8	3

		MCI-MCI(year of education)			MCI-AD dementia(baselineMMSE)			MCI-MC	I(baseline	MMSE)	MCI- type	follow- up(Y)	Patient origin
Author	Year	n2	mean2	S2	n1	mean1	S1	n2	mean2	S2			
Tierney	1996	78	14.3	3.2	29	26.6	0.3	78	28	0.2	mix	2	North America
Korf	2004	38	10.5	3.3	37	26.2	2.5	38	27.5	3.1	mix	8	Europe
Devanand	2005	101	15.4	4.1	35	26.4	1.9	101	28.1	1.8	mix	5	North America

Drzezga	2005	18	11.1	3.2	12	25.9	2.1	18	27.6	1.5	mix	1	Europe
Randall Griffith	2005	34	13.33	2.08	10	28.25	1.36	34	28.47	1.73	aMCI	4	North America
Stoub	2005	44	15	3.1	14	26.9	1.8	44	28.5	1.5	aMCI	5	North America
Dong Young Lee	2006	55	4.3	5	_	-	_	-	-	_	mix	3	Asia
Bouwman	2006	-	_	_	33	25.4	_	26	26.5	_	mix	4	Europe
Herukka	2006	-	_	_	33	23.91	2.69	45	24.09	2.49	mix	5	Europe
Tapiola	2006	47	6.7	1.5	13	23.3	2.3	47	24.1	2.6	mix	3	Europe
Barabash	2007	-	_	-	-	-	_	-	-	_	aMCI	4	Europe
Forsberg	2007	14	12	4.2	7	27	1.3	14	28.9	0.9	mix	2	Europe
Luca Rozzini	2007	79	7.9	3.7	40	26.1	1.9	79	27.3	1.8	aMCI	1	Europe
Anna Caroli	2007	14	8.6	3.6	9	26.8	1.8	14	27	2	aMCI	3	Europe
Ewers	2007	_	_	_	8	24.3	3.6	9	26.7	1.9	aMCI	3	Europe
Ewers	2007	-	_	-	19	27.8	1.1	19	28.8	1.2	aMCI	3	Europe
Ewers	2007	-	_	-	13	25.5	1.1	9	27.2	1.4	aMCI	3	Europe
Ewers	2007	-	_	-	3	27.7	2.3	8	26.5	2	aMCI	3	Europe
Fleisher	2007	327	14.97	2.84	_	-	_	_	_	_	aMCI	3	North America
Howard H Feldman	2007	401	11.2	4.2	109	24.7	3.7	401	27.5	2.1	mix	3	North America
Gavrilova	2008	-	_	-	5	26.6	0.6	31	28	0.9	mix	2	Europe
Kester	2011	58	5	1	42	26	3	58	27	2	mix	2	Europe
Davatzikos	2011	-	_	-	69	25.8	2.18	170	27.1	1.82	mix	3	Europe
Jieping Ye	2012	177	15.65	3.06	142	26.62	1.71	177	27.38	1.75	mix	4	North America
Vosa	2012	105	10.7	3.2	48	25.8	2.8	105	26.9	2.6	mix	5	Europe
Prestia	2015	-	_	_	29	26.76	1.6	44	27.5	6.18	mix	1	Europe
Spampinato	2016	-	-	-	-	-	—	-	-	_	aMCI	3	Europe
Lei Zheng	2016	-	-	-	75	23.12	1.5	86	25.89	1.4	aMCI	2	Asia
Falahati	2017	75	16.2	2.8	70	26.6	1.7	75	27.5	1.7	mix	3	Europe
Hansson O	2006	-	-	-	57	26.8	1.4	56	27.3	1.8	mix	7	Europe
Spulber	2012	48	6.81	2.33	12	23.14	2.1	48	26.12	2.5	mix	2	North America
Liu	2007	82	9.8	4.9	42	23.7	3.6	82	25.9	3.1	mix	3	Asia
Gabryelewicz	2007	-	_	—	23	26.6	2.1	82	27.4	1.5	mix	3	Europe
Erten-Lyons	2006	17	15	3.1	23	27.13	2.05	17	27.5	1.87	mix	7	North America
Wang	2005	39	11.7	3.3	19	24.4	2.1	39	26.6	2.6	aMCI	2	Asia
Hsiung	2004	_	_	_	_	-	_	_	-	_	mix	5	North America
Amieva	2003	-	-	-	29	27.3	1.2	61	27.9	1.6	mix	2	Europe
ALBERT	2001	_	_	_	_	_	_	_	_	_	mix	3	North America
Varatharajah	2019	_	_	_	_	_	_	_	_	_	mix	3	North America
Meester(A)	2018	291	13.3	4.3	63	28	1.5	291	28.4	1.7	mix	3	North America
Meester (C)	2018	186	12.5	2.8	83	27.6	1.8	186	28.2	1.6	mix	3	Europe
Meester(B)	2018	46	10.8	4.2	5	28.8	1.9	46	28.3	1.5	mix	3	Europe
Mosconi	2004	29	10	5	8	26.7	1.3	29	28.3	1.4	aMCI	1	Europe

## Literature Quality Assessment



Each of the 43 included studies was evaluated using the QUADAS-2. Review Manager 5.2 was used to assess the literature quality (Figure 2).

# **Meta-Analysis Results**

With 38 articles enrolled for this meta-analysis, the predictive value of APOE4+ for MCI-to-AD dementia was analyzed as a whole as well as in different subgroups. In general, it was not statistically significant (sensitivity: 0.59, 95%CI: 0.56-0.61; specificity: 0.63,

# **APOE4+ and Progressing Interval Time**

95%CI: 0.61-0.64; AUC: 0.62; I squared: 55.8%; tau squared: 0.24).

# APOE4+ and Ages

The predictive value of APOE4+ for MCI people aged  $\geq$ 70 progressing to AD dementia was higher than that of those aged <70. (sensitivity: 0.60, 95%CI: 0.62-0.67; specificity: 0.60, 95%CI: 0.58-0.62; AUC 0. 65; sensitivity 0.50, 95%CI: 0.45-0.55; specificity 0.64, 95%CI: 0.60-0.67; AUC: 0. 56, respectively).



Figure 3: The diagnostic value of APOE4+ for MCI people aged 70 and with internal time of 5 years to AD dementia.

As indicated in Figure 3, it was 5 years as the interval time for MCI people with APOE4+ progressing to AD dementia, with SROC 0.78, the pooled sensitivity 0.57 (95%CI: 0.50-0.64) and specificity 0.73 (95%CI: 0.68-0.77). Furthermore, the predictive value of APOE4+ for MCI-to-AD was higher in MCI people aged  $\geq$ 70 progressing to AD dementia in 5 years than that in other subgroups (sensitivity: 0.71, 95%CI: 0.63-0.79; specificity: 0.71, 95%CI: 0.65-0.76; AUC:

0.78). It was insignificant about other progressing intervals such as 1 year (sensitivity: 0.60, 95%CI: 0.49-0.70; specificity: 0.61, 95%CI: 0.53-0.68; AUC: 0.63); 2 years (sensitivity: 0.50, 95%CI: 0.43-0.56; specificity: 0.59, 95%CI: 0.54-0.64; AUC: 0.54); 3 years (sensitivity: 0.61, 95%CI: 0.57-0.64; specificity: 0.62, 95%CI: 0.60-0.64; AUC: 0.63); 4 years (sensitivity: 0.62, 95%CI: 0.55, 0.68; specificity: 0.60, 95%CI: 0.54-0.66; AUC: 0.64); and over 5 years (sensitivity: 0.59, 95%CI: 0.50, 0.68; specificity: 0.61, 95%CI: 0.48-0.67; AUC: 0.63). Legend: APOE4+ diagnostic value for MCI people aged  $\geq$ 70 who trended to progress to AD at the time interval of five years (A: AUC; B: sensitivity; C: specificity).

# **APOE4+ and Geographic Area**

Among different geographic areas the predictive-value of APOE4+ for MCI-to-AD dementia was significantly. In Asia, the sensitivity was 0.64, 95%CI, 0.55-0.71; specificity, 0.52, 95%CI, 0.46-0.58; and AUC, 0. 63. In North America, the sensitivity was 0.57, 95%CI, 0.53-0.61; specificity, 0.67, 95%CI, 0.65-0.69; and AUC, 0. 67. In Europe, the sensitivity was 0.59, 95%CI, 0.56-0.63; specificity, 0.60, 95%CI, 0.57-0.62; and AUC, 0. 62.

# APOE4+ and MCI Type

The predictive value of APOE4+ was higher in aMCI than in mix-MCI progressing to AD dementia (sensitivity: 0.66, 95%CI: 0.62-0.69; specificity: 0.61, 95%CI: 0.58-0.65; AUC: 0. 67, vs. sensitivity: 0.55, 95%CI: 0.52-0.58; specificity: 0.63, 95%CI: 0.61-0.65; AUC: 0.62).

# **APOE4+ and Educational Years**

The predictive value of APOE4+ for MCI-to-AD dementia was higher in those with  $\geq$ 12 years of education than those with <12 years of education (sensitivity: 0.63, 95%CI: 0.59-0.66; specificity: 0.64, 95%CI: 0.62-0.67; AUC: 0. 67, vs. sensitivity: 0.56, 95%CI: 0.51-0.61; specificity: 0.56, 95%CI: 0.53-0.59; AUC: 0. 58).

#### **APOE4+ and Multi-Factors**

As to APOE4+, the predictive value of MCI-to-AD dementia was not improved when plus all relative predictive factors, such as MCI people aged  $\geq$ 70 plus being North American (sensitivity: 0.66, 95%CI: 0.62-0.70; specificity: 0.61, 95%CI: 0.58-0.64; AUC: 0. 68); MCI people aged  $\geq$ 70 plus being of aMCI type (sensitivity: 0.67, 95%CI: 0.62-0.71; specificity: 0.61, 95%CI: 0.57-0.65; AUC: 0. 68); and MCI people aged  $\geq$ 70 plus  $\geq$ 12 years of education (sensitivity: 0.68, 95%CI: 0.64-0.72; specificity: 0.62, 95%CI: 0.59-0.65; AUC: 0. 70).

# The Risk of APOE4+ for MCI -to -AD

As indicated by the results, an association was observed between APOE4+ and MCI-to-AD dementia (RR: 1.49; 95%CI: 1.33-1.67). The subgroup analysis showed that the heterogeneity was clinic heterogeneity caused by age, geographicarea, MCI type and research design (Figure 4). In the age subgroup, those who were aged  $\geq$ 70 (RR: 1.56; 95%CI: 1.36-1.78) had a higher risk than those who were aged <70 (RR:1.25; 95%CI: 0.99-1.59). As to the progressing interval time, different intervals were found to be correlated with the different risks of APOE4+ for MCI-to-AD dementia. The risk was higher at the time interval of 5 years (RR: 2.24; 95%CI: 1.43-3.50) than the others such as 1 year (RR: 1.50; 95%CI: 1.17-1.93); 2 years (RR:1.13; 95%CI: 0.83-1.55); 3 years (RR:1.47, 95%CI: 1.25-1.74);4 years (RR:1.57; 95%CI:1.31-1.88); 7 years (RR:1.46, 95%CI: 1.09-1.96); and 8 years (RR:1.51; 95%CI: 0.94-2.42). As indicated by the results of APOE4+ in the geographic area subgroup, Asian's RR was 1.58, and 95%CI, 0.85-2.92; North American's RR was 1.67, and 95%CI, 1.37-2.04; and European's RR was 1.40, and 95%CI, 1.24-1.58. In the MCI type subgroup, aMCI's RR was 1.67, and 95%CI, 1.51-1.85; and mix-MCI's RR was 1.44, and 95%CI, 1.24-1.67. In the education-year subgroup, ≥12years of education showed that the RR was 1.69, and 95%CI, 1.40-2.04, while <12 years of education showed that the RR was 1.32, and 95%CI, 1.06-1.63. In the research design subgroup, the case-control studies showed that the RR was 1.42, and 95%CI, 1.25-1.62, while the cohort studies indicated that the RR was 1.50, and 95%CI, 1.31-1.73. Legend: A. demonstrated subgroup (European, Asia and North American), B. demonstrated age subgroup (≥70 & <70), C. demonstrated subgroup (aMCI & mixMCI), C. demonstrated research design subgroup (case-control & cohort studies). To all case-control studies was applied OR, RR the estimator for OR.

# **Publication Bias**

The funnel plots appeared to be symmetric, showing no evidence of publication bias sensitivity analysis. The Begg's test results indicated that the Kendall's score(P-Q)=95, Z=0.99, and P=0.32, and Egger's test results showed P=0.11, both of them indicating no publication bias (Figure 5).

# Discussion

Although there were two meta-analyses [17-18] which had calculated the effect of APOE4+ on MCI-to-AD dementia, the results were significantly different between the two studies, with the OR 2.29 (95% CI: 1.88-2.80) vs. 1.84 (95%CI:1.59-2.14). No metaanalysis was reported on the predictive value of APOE4+ for MCto-AD. In the current study, we analyzed the predictive value of APOE4+ for MCI-to-AD dementia in different subgroups. Although as a whole the predictive value of APOE4+ for MCI-to-AD was not statistically significant, it was in the different subgroups. In the MCI people aged ≥70, APOE4+ had a high predictive value for MCI-to-AD dementia. Previous studies [19,62,63] had indicated that there was a correlation between APOE ε4+ and cognition decline in older people, but the exact age was unclear. The results of our metaanalysis indicated that the age of 70 was the cut-off point, and that the APOE4+ predictive sensitivity was high in those who were aged  $\geq$ 70, which suggested that APOE4+ was valuable for MCI people aged  $\geq$ 70 to predict the progression of MCI to AD dementia.



Figure 4: The forest plot in different subgroups of MCI with APOE4+ to AD dementia.

In the current study, we discovered that predictive value of APOE4+ for MCI-to-AD was significantly different in different geographic areas, as indicated by the evidence that the risk of MCI-to-AD dementia was higher in North America than in Europe and Asia. The difference was reported to be caused by APOE gene which variated among different geographic regions. APOE4+ showed a more significant increasing tendency in North European populations than in Asian and Oceanian ones [64,65], which suggested that APOE4+ could be more valuable for MCI people in North America to predict MCI-to-AD dementia. It was also found that the predictive value of APOE4+ for aMCI progressing to AD

dementia was high. Some literatures have demonstrated that aMCI is a high risk of MCI-to-AD dementia [64,66], which agreed with our conclusion. In fact, some studies [67-69] have testified that APOE4+ is correlative with aMCI, likely to modulate the large-scale brain network in aMCI subjects, as elucidated in a recently study reporting that the risk of memory decline was associated with A $\beta$  and APOE4+ at each age. Therefore, our findings suggested that APOE4+ was more valuable for aMCI people to predict MCI-to-AD dementia. Moreover, the predictive value of APOE4+ for MCI-to-AD dementia was high in those who had  $\geq$ 12 years of education. Some studies [70,71] have found that a higher education level may delay

the progression of MCI to AD dementia. Our findings indicated that the predictive value of APOE4+ was high in MCI people with more years of education. Although a previously reported study found that APOE  $\varepsilon$ 4 might not be associated with years of education [72], our findings still suggested that APOE4+ was valuable for MCI people who had  $\geq$ 12 years of education to predict MCI-to-AD dementia.

Furthermore, we found that the time interval for MCI-to-AD dementia could be 5 years, especially for MCI people with APOE4+ and aged  $\geq$ 70. The risk estimated by RR of APOE4+ for MCI-to-AD dementia changed at different time intervals, with the highest at the 5th year, which suggested that APOE4+ was more valuable for MCI people aged  $\geq$ 70 to predict MCI-to-AD dementia at the time interval of 5 years. Additionally, the predictive value of APOE4+ showed no significance for MCI-to-AD dementia when the multiple-factor superposition involved MCI people aged  $\geq$ 70 plus being North American, or plus being aMCI, or plus  $\geq$ 12 years of education. This suggests that a part of variable may not help make the incremental effect when we predict the progression of MCI to AD dementia by a multiple-factor superposition.

#### Limitations

There was high heterogeneity in our meta-analysis, which needs to be overcome with a bigger collection of relevant literatures in the future. Additionally, the high risk of bias in literature quality is a limitation, too.

## Conclusion

The predictive value of APOE4+ for MCI-to-AD dementia was valuable for MCI people in North America, the subtype of aMCI and  $\geq$ 12 years of education. As a strong implication, it may take less than 5 years for MCI people aged  $\geq$ 70, who carried the gene of APOE4+, to progress to AD dementia (sensitivity: 0.71, 95%CI: 0.63-0.79; specificity: 0.71, 95%CI: 0.65-0.76, AUC: 0.78).

## **Conflict of Interest**

The authors declare no conflict of interests.

## **Disclosure Statement**

The authors have no actual or potential conflicts of interest.

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#### **Author Contribution**

ZL, WXQ conceived and designed the project. YJ, XHZ collected data. YJ wrote the manuscript. YJ, LXY and SHJ prepared Figures 1-5. All authors reviewed the manuscript.



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