Meta-analysis of the association between *CD33* and Alzheimer's disease

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Background: The cluster of *differentiation 33* (*CD33*) gene is compelling among the susceptibility genes of Alzheimer's disease (AD) in Genome-wide association study (GWAS). Researches of the relationship between AD and polymorphism in *CD33* have showed conflicting results. In order to more precisely evaluate whether *CD33* variants are associated with AD, we performed the meta-analysis presented in this manuscript.

Methods: We searched from three databases including PubMed, Cochrane library and EMbase for related case-control researches based on criteria of determination. A total of 18 case-control studies, containing 50,030 cases and 77,405 controls were involved in *CD33* rs3865444 polymorphism. And a total of 4 case-control studies, containing 826 cases and 984 controls were involved in *CD33* rs3826656 polymorphism.

Results: This study demonstrated that different variants in *CD33* were associated with AD (rs3865444: OR =0.94; 95% CI, 0.90–0.98, P<0.01; rs3826656: OR =0.94; 95% CI, 0.62–1.41, P<0.01). We made subgroup analysis which was stratified by race. There were protective associations in Caucasians but not in Asians among *CD33* rs3865444 polymorphism (Caucasians: OR =0.92; 95% CI, 0.90–0.94, P=0.05; Asians: OR =0.87; 95% CI, 0.65–1.17, P<0.01).

Conclusions: The *CD33* rs3865444 polymorphism could be a protective factor in AD. Meanwhile, there was no association between the *CD33* rs3826656 polymorphism and AD. Further confirmation is needed in larger and better-designed researches.

Keywords: Meta-analysis; *cluster of differentiation 33* (*CD33*); Alzheimer's disease (AD)

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Introduction

Alzheimer's disease (AD) is a complicated neurodegenerative disease with progressive cognitive impairment common in elderly people. In 2006, the prevalence of AD was 26.6 million around the world, and the number of AD will quadruple by 2050 (1). AD consists of early-onset AD (EOAD) and late-onset AD (LOAD). LOAD, which accounts for the majority of AD, is the result of interaction between environmental and genetic factors (2). Genetic factors play an important role in it, and the heritability is estimated to be up to 80% (3-6). Up to now, the *apolipoprotein E* (*APOE*) gene is the only one gene that was certainly recognized to increase the risk of LOAD, but the *APOE ε4* gene can only interpret 27.3% about the risk of AD onset (7-10). Therefore, further efforts are needed to look for risk genes other than APOE.

The cluster of *differentiation 33* (*CD33*) gene is an immune function protein located in 19p13.33 with several functions, such as cell adhesion, anti-inflammatory signaling, and endocytosis functions (11). In addition, it is one of the members of the sialic acid-binding Ig-like lectin

(SIGLEC) family (12). Several studies have investigated the important role of *CD33* rs3865444 polymorphism in AD. As for rs3865444, the risk allele (C) was related with the overexpression of *CD33* on mononuclear cell surface, which is involved in the pathogenesis of AD through down-regulation of β-amyloid (Aβ) internalization, accumulation of neuritic amyloid pathology, and regulation of microglia levels (13). Both lines of evidence indicate that *CD33* gene could play an important role in susceptibility to AD.

In 2011, three large-scale genome-wide association studies (GWAS) conducted by Hollingworth *et al.* (14), Carrasquillo *et al.* (15), and Naj *et al.* (16) confirmed that the gene *CD33* showed significantly correlation with LOAD in Europe. After that, the associations between AD and the variants of *CD33* have become the focus of many studies. But the conclusions of these studies differ from each other. But the conclusions of these studies are inconsistent (7,14-29). To better illuminate the associations between *CD33* and the susceptibility to AD, a meta-analysis was conducted by analyzing and summarizing the relevant studies.

Methods

Literature search

We searched literature in PubMed, EMbase, and Cochrane library up to 1 October 2017. Medical Subject Heading (MESH) terms were used: (*CD33*) AND {[(Alzheimer's) OR dementia] OR Alzheimer disease}. Additional studies were screened manually in each qualifying study.

Inclusion criteria

We chose the studies meeting the following criteria: (I) studies must evaluate the associations between polymorphism of *CD33* and the susceptibility to AD; (II) the research type of the selected studies was case-control design; (III) adequate information should be accessible, such as the study sample size of each research group, allele or genotype frequencies, OR, 95% CI and the P value; (IV) the diagnosis of AD should meet the clinical criteria set by the World Health Organization.

Data extraction

According to the specified selection criteria, all data were extracted independently by two investigators. The following data were extracted: (I) name of the first author, (II) publication year, (III) country and ethnicity of origin, (IV) numbers of cases and controls, (V) allele frequency distributions and numbers of different genotypes, (VI) the OR with 95% CI of *CD33*. Newcastle-Ottawa quality scale (NOS) was selected to evaluate the quality of eligible studies: (I) the selection; (II) the comparability; (III) the exposure. Studies with a score larger than seven points were considered to be of high quality.

Statistical analysis

Stata 11.0 software version 11.0 (StataCorp LP, College Station, TX, USA) and R software [Version 3.2.2, Copyright(C) 2014 The R Foundation for Statistical Computing] were selected for statistical analysis. Hardy-Weinberg equilibrium (HWE) was used to verify the representation of the selected studies. We conducted a subgroup analyses on the basis of ethnicity (Asian, Caucasian and Negroid). Statistical heterogeneity could be evaluated by Cochran's Q statistic and I^2 Statistic test. When significant heterogeneity (PQ >0.10 and I^2>50%) was observed, the random-effects model was carry out; in addition, the fixed-effects model was adopted. In order to assess the stability of the results, we conducted sensitivity analysis by omitting a single study each time. Funnel plots were generated by the R software to evaluate the potential publication bias. And publication bias was also checked by Egger's linear regression analysis and Begg's rank correlation test, and P<0.05 indicated a significant publication bias.

Results

Study inclusion and characteristics

In the present meta-analysis, a systematic overview of relevant studies to evaluate the risk between gene *CD33* and the susceptibility to AD have been accomplished. Eighty-five articles were searched from PubMed, EMbase, Cochrane library and other sources, such as using a manual retrieval from relevant studies. After the initial scan of titles and abstracts, 39 unrelated studies were excluded because they were not relevant to AD or they were duplicate publications. According to the inclusion standards set in advance, 28 publications were excluded. After our screening, 18 articles on relevant SNPs were included in this meta-analysis (*Figure 1*). Eventually, 38 researches investigating the single nucleotide polymorphism (SNP) of rs3865444

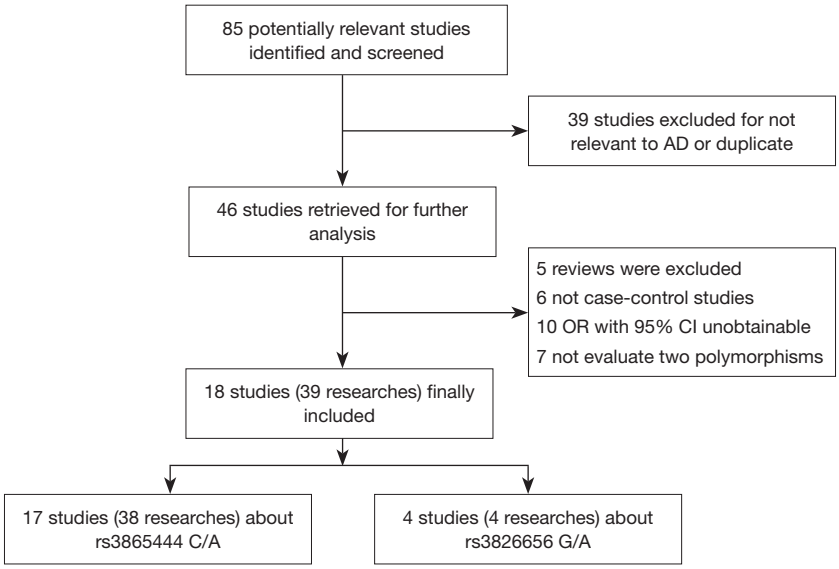

Figure 1 Flow chart of meta-analysis for exclusion or inclusion of individual articles. AD, Alzheimer's disease; CI, confidence intervals; OR, odds ratio.

and 4 researches investigating the SNP of rs3826656 were included. The characteristics of these involved studies were presented in the *Tables 1*,*2*.

CD33 rs3865444 SNP and AD susceptibility

We studied the correlation between SNP rs3865444 of *CD33* and AD susceptibility in this meta-analysis. Among the 38 enrolled researches, 31 were performed in Caucasian population, 6 were performed in Asian population and only one was performed in Negroid population. In the pooled OR, we can observe significant heterogeneity. We used a random-effect model to assess the overall effect of the C/A allele model (I^2=60%, P<0.01), and the A mutant of rs3865444 was found to be significantly associated with AD prevention (OR =0.93; 95% CI, 0.90–0.97; *Figure 2*). Considering the difference of ethnicity, we made subgroup analyses. The existence of high heterogeneity could be identified. In the stratified analysis among Caucasian ethnicity, the heterogeneity was decreased (I^2=33%, P=0.04), and a fixed-effect model could be used. Similarly, the association of rs3865444 and AD susceptibility was not verified (OR =0.91; 95% CI, 0.89–0.93; *Figure 3*). Besides, in the stratified analysis among Asian ethnicity, the heterogeneity was increased (I^2=88%, P<0.01), and a random-effect model may be used. But the association between rs3865444 and AD susceptibility turned into no significance (OR =0.87; 95% CI, 0.65–1.17; *Figure 4*).

CD33 rs3826656 SNP and AD susceptibility

We did a research about the association between *CD33* rs3826656 SNP and AD susceptibility in a cumulative meta-analysis. Among the 4 studies on rs3826656, 3 were conducted in the Asian population and only one was performed in Caucasians. We used a random-effect model to evaluate the effect of the G/A allele model (I^2=80%, P<0.01). The pooled ORs identified no correlation between SNP rs3826656 and AD in the present meta-analysis (OR =0.94; 95% CI, 0.62–1.41; *Figure 5*).

Publication bias and sensitivity analysis

The funnel plot for the two SNPs of *CD33* exhibited relative symmetry (*Figures S1*,*S2*). There were no statistically significant publication bias in SNP rs3865444 (PBegg's = 0.186, PEgger's =0.643; *Figure S3*). Similarly, there was no publication bias in SNP rs3826656 (PBegg's =1, PEgger's =0.892; *Figure S4*). Sensitivity analysis of *CD33* rs3865444 SNP was performed by continuously excluding individual studies to test the effect of individual data on the pooled ORs, of which the results revealed that no individual study can significantly affect the overall value of ORs and 95% CIs (*Table 3*). As for *CD33* rs3826656 SNP, the results

Table 1 Characteristics of included studies for *CD33* rs3865444 gene

No.	First author	Year	Country	Ethnicity	Case	Control	OR (95% CI)
1	Deng	2012	China	Asians	190	193	0.48 (0.351–0.655)
2	Tan	2013	China	Asians	612	612	1.442 (1.182–1.759)
3	Miyashita	2013	Japan	Asians	891	844	1.04 (0.92–1.18)
4	Chung	2013	Korea	Asians	290	554	0.7 (0.51–0.96)
5	Jiao	2014	China	Asians	229	318	1.11 (0.834–1.478)
6	Mao	2015	China	Asians	126	129	0.664 (0.43–1.028)
7	Logue	2011	USA	Negroes	513	496	1 (0.7–1.29)
8	Carrasquillo (Jacksonville)	2011	USA	Caucasians	492	920	0.82 (0.68–0.98)
9	Carrasquillo (Rochester)	2011	USA	Caucasians	312	1,577	0.88 (0.72–1.08)
10	Carrasquillo (Autopsy)	2011	USA	Caucasians	298	97	0.84 (0.57–1.24)
11	Naj (ADGC-GWAS)	2011	USA	Caucasians	8,309	7,366	0.88 (0.84–0.93)
12	Naj (ADGC-REP)	2011	USA	Caucasians	3,531	3,565	0.91 (0.85–0.99)
13	Hollingworth (GERAD1)	2011	Europe	Caucasians	3,333	1,225	0.91 (0.82–1)
14	Hollingworth (EADI1)	2011	Europe	Caucasians	2,025	5,328	0.89 (0.82–0.97)
15	Hollingworth (deCODE)	2011	Europe	Caucasians	925	612	0.85 (0.68–1.04)
16	Carrasquillo	2011	Norway	Caucasians	327	541	0.89 (0.70–1.14)
17	Carrasquillo	2011	Poland	Caucasians	467	187	1 (0.72–1.37)
18	Carrasquillo (ARUK)	2011	Europe	Caucasians	642	730	0.98 (0.83–1.17)
19	Lambert	2013	USA	Caucasians	572	1,340	0.93 (0.8–1.08)
20	Lambert (ADGC)	2013	Europe	Caucasians	10,273	10,892	0.89 (0.86–0.92)
21	Lambert (CHARGE)	2013	Europe	Caucasians	1,315	12,968	1 (0.92–1.09)
22	Lambert (EADI)	2013	Europe	Caucasians	2,243	6,017	0.9 (0.83–0.98)
23	Lambert (GERAD)	2013	Europe	Caucasians	3,177	7,277	0.89 (0.77–1.03)
24	Lambert	2013	Austria	Caucasians	210	829	1.08 (0.82–1.42)
25	Lamber	2013	Belgium	Caucasians	878	661	0.95 (0.79–1.14)
26	Lambert	2013	Finland	Caucasians	422	562	1.08 (0.89–1.31)
27	Lambert	2013	Germany	Caucasians	972	2,378	1 (0.89–1.12)
28	Lambert	2013	Greece	Caucasians	256	229	0.79 (0.52–1.20)
29	Lambert	2013	Hungary	Caucasians	125	100	0.94 (0.6–1.47)
30	Lambert	2013	Italy	Caucasians	1,729	720	1.12 (0.97–1.29)
31	Lambert	2013	Spain	Caucasians	2,121	1,921	0.94 (0.85–1.04)
32	Lambert	2013	UK	Caucasians	490	1,066	1 (0.84–1.19)
33	Lambert	2013	Sweden	Caucasians	797	1,506	0.99 (0.87–1.13)
34	Walker	2014	USA	Caucasians	97	96	1.13 (0.74–1.70)
35	Carrasquillo	2014	USA	Caucasians	54	2,523	0.86 (0.56–1.32)
36	Omoumi	2014	Canada	Caucasians	428	524	0.62 (0.48–0.8)
37	Moreno	2017	Colombian	Caucasians	280	357	1.12 (0.87–1.42)
38	Lígia	2017	Brazil	Caucasians	79	145	0.7 (0.46–1.09)

CI, confidence intervals.

Table 2 Characteristics of included studies for *CD33* rs3826656 gene

No.	First author	Year	Country	Ethnicity	Case	Control	OR (95% CI)
1	Yuan	2012	China	Asians	191	180	0.479 (0.263–0.870)
2	Jiao	2014	China	Asians	229	318	0.839 (0.648–1.086)
3	Mao	2015	China	Asians	126	129	1.760 (1.185–2.615)
4	Moreno	2017	Colombian	Caucasians	280	357	0.620 (0.43–0.89)

CI, confidence intervals.

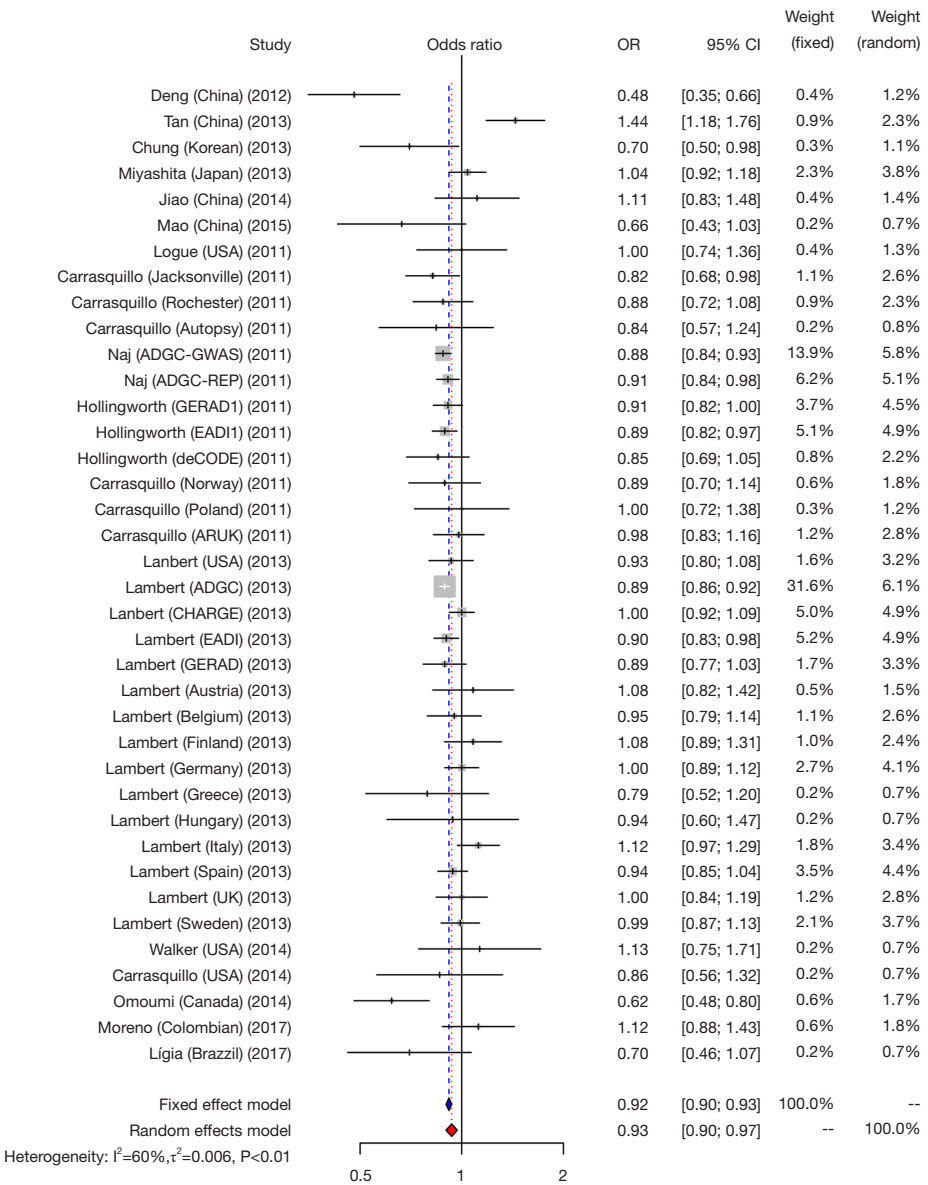

Figure 2 The forest plot of *CD33* rs3865444 genetic variation with AD in combined population (gene model comparison: C *vs.* A). Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 0.93 (95% CI, 0.90–0.97; P<0.01) in the random-effects model. Values less than 1 denote a decreased risk for AD with the A allele. AD, Alzheimer's disease; CI, confidence intervals; OR, odds ratio.

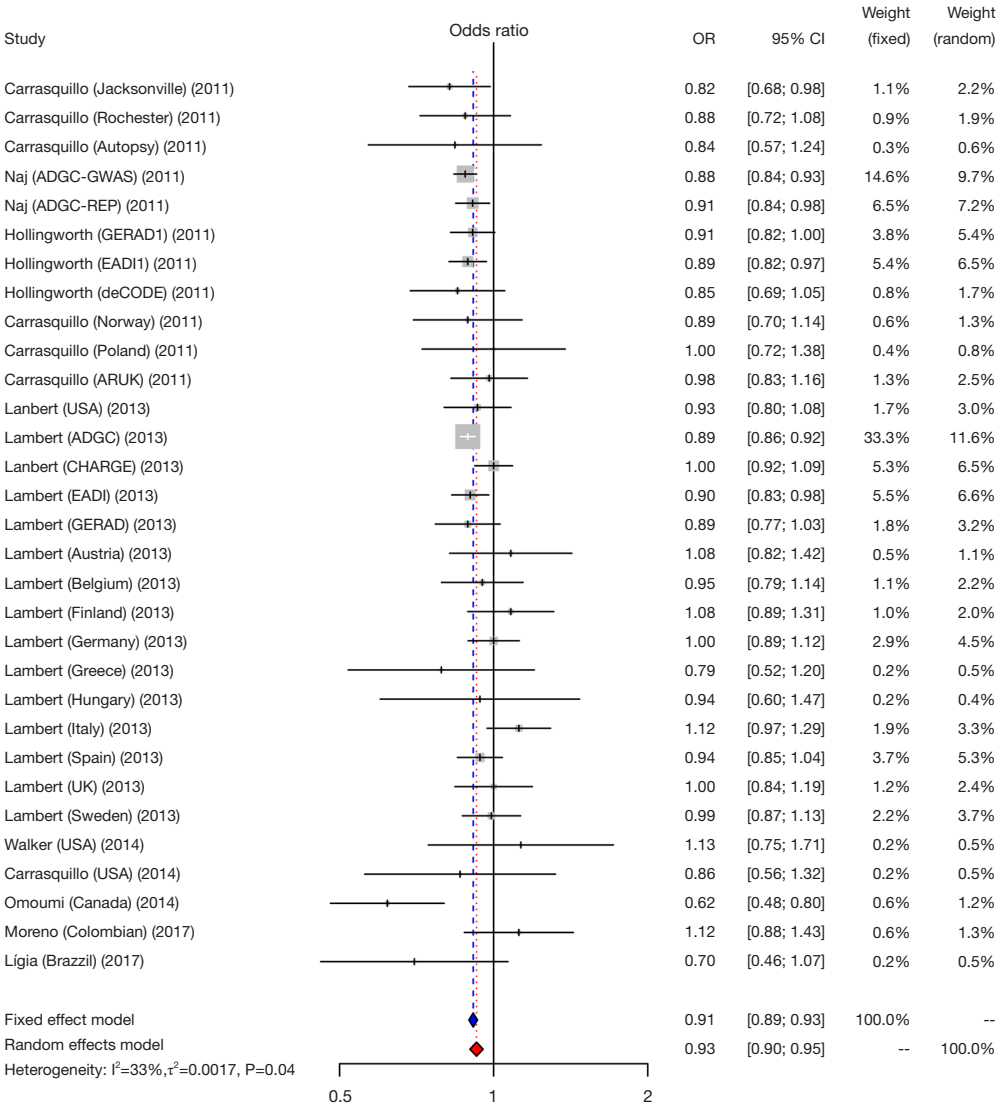

Figure 3 The forest plot of *CD33* rs3865444 genetic variation with AD in Caucasian population (gene model comparison: C *vs.* A). Horizontal lines are 95% CI. The contrast has an OR of 0.91 (95% CI, 0.89–0.93; P=0.04) in the fixed-effects model. AD, Alzheimer's disease; CI, confidence intervals; OR, odds ratio.

remained as insignificant as before.

Discussion

Our meta-analysis summarized the evidence to date of the links between common polymorphisms of *CD33* gene and the risk of AD. The variant of rs3865444 was identified to be significantly associated with lower risk of AD, while no correlation was showed of the rs3826656 SNP with the risk of AD. We believe that our findings containing the latest published studies will be meaningful for future genetic studies on AD and *CD33* gene, which may be a potential candidate gene for AD susceptibility.

Since July 2011, related studies on the association between the *CD33* gene polymorphisms and AD have been carried out all over the world with subjects in different populations, such as Caucasian, Asian and Negro populations. Because of the few number of articles about Negroid, no subgroup analysis on it was done. In China, Tan *et al.* in 2013 showed that the polymorphism of *CD33* rs3865444 was a risk factor for AD (OR =1.442; 95% CI, 1.182–1.759) (17), which was different from results in

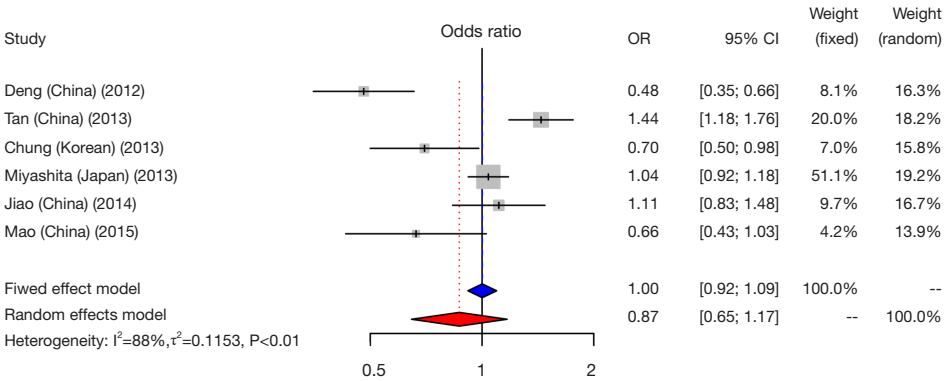

Figure 4 The forest plot of *CD33* rs3865444 genetic variation with AD in Asian population (gene model comparison: C *vs.* A). Horizontal lines are 95% CI. The contrast has an OR of 0.87 (95% CI, 0.65–1.17; P<0.01) in the random-effects model. AD, Alzheimer's disease; CI, confidence intervals; OR, odds ratio.

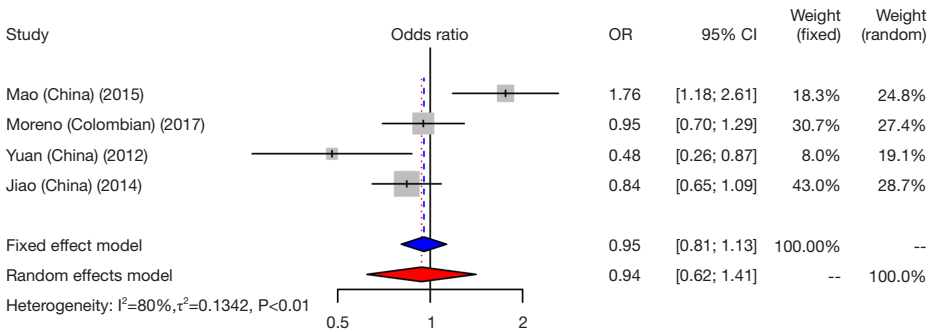

Figure 5 The forest plot of *CD33* rs3826656 genetic variation with AD in combined population (gene model comparison: G *vs.* A). Horizontal lines are 95% CI. The contrast has an OR of 0.94 (95% CI, 0.62–1.41; P<0.01) in the random-effects model. AD, Alzheimer's disease; CI, confidence intervals; OR, odds ratio.

most Caucasian population. But in China, another study conducted by Deng *et al.* obtained an opposite conclusion compared with that of Tan *et al.* (OR =0.48; 95% CI, 0.351–0.655) (20). In 2013, a meta-analysis conducted by Lambert showed the evidence that the variants of rs3865444 were found to be significantly associated with lower risk of AD in Caucasian population (OR =0.94; 95% CI, 0.91–0.96) (30). Considering the inconsistent results, ethnic subgroups were used to eliminate possible ethic differences. As for the polymorphism of *CD33* rs3826656, Mao *et al.* made a meta-analysis in China to identify whether SNP rs3826656 was associated with increased risk of AD (OR =1.39; 95% CI, 1.09–1.76) (31). In order to further harmonize these contradictory findings and to acquire a more accurate conclusion about the two SNPs of *CD33* gene, an updated meta-analysis was conducted.

Based on those recent studies on the role of rs3865444 SNP in pooled population, our results showed a significant link between risk allele (A) and lower risk of AD. In a subgroup analysis, the results of the present study in Caucasian population supported that rs3865444 variant had protective association with AD. As predicted, the result was the same as that of the study conducted by Lambert (30). In Asian population, the correlation between rs3865444 gene polymorphism and the incidence of AD could not be determined. We couldn't agree with the conclusions made by Tan *et al.* and Deng *et al.* Besides, there was only one study about the population of Negroid ethnicity with limitation of the sample size, which might not provide sufficient data in Negroid population. Large-scale case-control studies in different ethnicities and regions need to be performed. With regard to rs3826656 gene polymorphism, there was no association between this gene locus and AD, which was different from the result drawn by Mao *et al.* (31). To our knowledge, our study offers a more systematic and higher-quality evidence to indicate

Table 3 Sensitivity analysis about *CD33* rs3865444 polymorphism of the meta-analysis

Study omitted	OR	95% CI	P-heterogeneity
Deng (China)	0.933	0.897–0.969	<0.01
Tan (China)	0.911	0.871–0.951	<0.01
Chung (Korea)	0.924	0.881–0.966	<0.01
Miyashita (Japan)	0.914	0.872–0.957	<0.01
Jiao (China)	0.917	0.874–0.959	<0.01
Mao (China)	0.923	0.881–0.965	<0.01
Logue (USA)	0.918	0.875–0.961	<0.01
Carrasquillo (Jacksonville)	0.923	0.880–0.966	<0.01
Carrasquillo (Rochester)	0.92	0.877–0.963	<0.01
Carrasquillo (Autopsy)	0.92	0.878–0.964	<0.01
Hollingworth (GERAD1)	0.92	0.878–0.964	<0.01
Hollingworth (EADI1)	0.921	0.876–0.965	<0.01
Hollingworth (deCODE)	0.921	0.878–0.924	<0.01
Carrasquillo (Norway)	0.92	0.877–0.963	<0.01
Carrasquillo (Poland)	0.918	0.876–0.961	<0.01
Carrasquillo (ARUK)	0.917	0.874–0.960	<0.01
Lambert (USA)	0.919	0.876–0.961	<0.01
Lambert (ADGC)	0.922	0.873–0.970	<0.01
Lambert (CHARGE)	0.915	0.872–0.958	<0.01
Lambert (EADI)	0.92	0.876–0.965	<0.01
Lambert (GERAD)	0.92	0.877–0.964	<0.01
Lambert (Austria)	0.917	0.874–0.959	<0.01
Lambert (Belgium)	0.918	0.875–0.961	<0.01
Lambert (Finland)	0.915	0.873–0.958	<0.01
Lambert (Germany)	0.916	0.873–0.959	<0.01
Lambert (Greece)	0.921	0.878–0.963	<0.01
Lambert (Hungary)	0.919	0.877–0.962	<0.01
Lambert (Italy)	0.912	0.871–0.954	<0.01
Lambert (Spain)	0.918	0.874–0.962	<0.01
Lambert (UK)	0.917	0.874–0.960	<0.01
Lambert (Sweden)	0.916	0.873–0.960	<0.01
Walker (USA)	0.918	0.874–0.960	<0.01
Carrasquillo (USA)	0.92	0.877–0.962	<0.01
Omoumi (Canada)	0.929	0.888–0.969	<0.01
Moreno (Colombian)	0.916	0.874–0.958	<0.01
Lígia (Brazil)	0.922	0.880–0.965	<0.01

CI, confidence intervals; OR, odds ratio.

the relationship between two SNPs of *CD33* and AD. In addition, we added several new studies which increased the total amount of subjects to raise the accuracy of outcomes. All included studies were published in authoritative journals after 2011, which identified that the research on the *CD33* gene polymorphisms were promising and novel.

We have to admit that some limitations in our meta-analysis should be illuminated. There were lots of polymorphisms in *CD33*, such as rs10419982 (32), rs273652 (22), rs35112940 (33) and so on. Because of lack of researches on these loci, our study, which only concentrated on two polymorphisms of *CD33*, may not fully represent the function of *CD33* gene. A larger range of studies are demanded to reinforce the representation of this gene.

It is likely that the *CD33* polymorphism will play an important role on the way to genetic susceptibility in the future. The effective therapeutic interventions for AD are still very limited and, therefore, we hope further research on gene *CD33* can offer a specific structural goal for the development of novel therapeutic approaches.

Conclusions

The SNP rs3865444 of *CD33* played a protective role in AD, and this protective role still existed in Caucasian population in the subgroup analysis. There were no association between SNP rs3826656 and AD. Further studies with large sample size should be done to confirm our findings.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

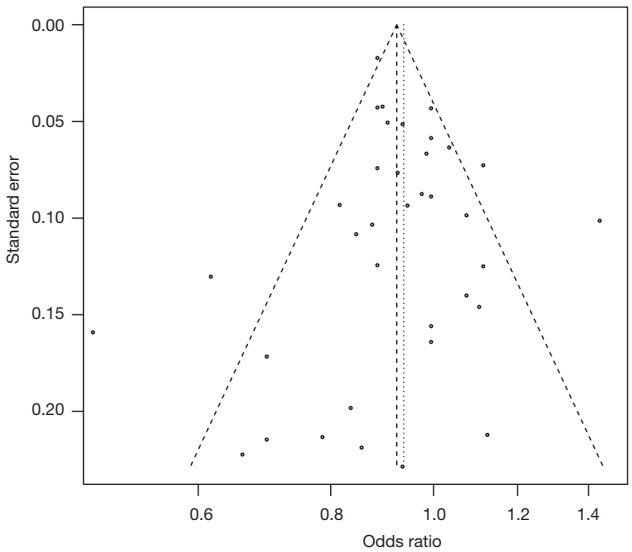

Figure S1 Funnel plots of *CD33* rs3865444 polymorphism in allele model. The shapes of the funnel plots revealed a degree of symmetry visually which indicated publication bias may not exist. Each point represents a separate study for the indicated association.

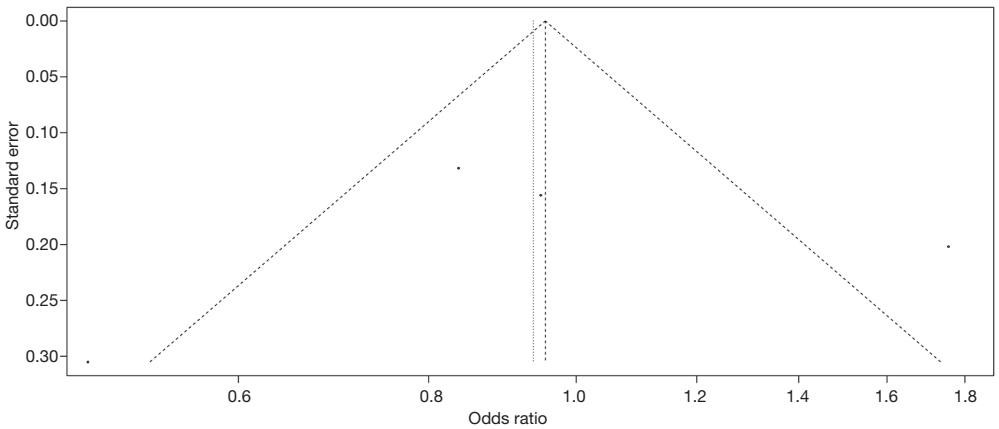

Figure S2 Funnel plots of *CD33* rs3826656 polymorphism in allele model. The shapes of the funnel plots revealed a degree of asymmetry visually which indicated publication bias may exist. Each point represents a separate study for the indicated association.

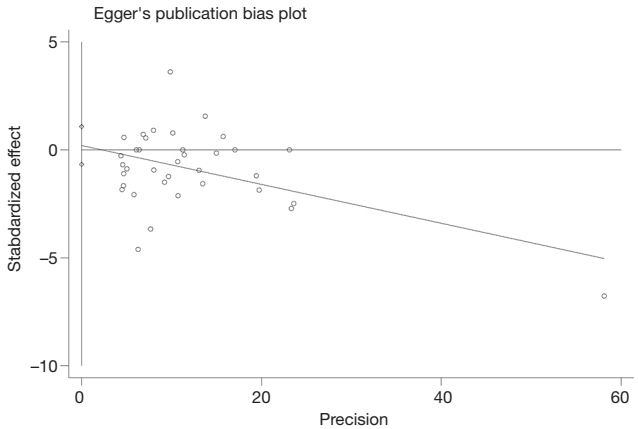

Figure S3 Egger's funnel plot for publication bias in studies on *CD33* rs3865444 polymorphism and Alzheimer's disease (gene model comparison: C *vs.* A).

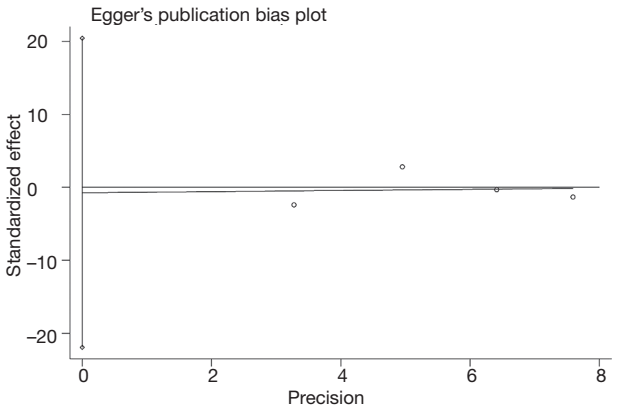

Figure S4 Egger's funnel plot for publication bias in studies on *CD33*rs3826656 polymorphism and Alzheimer's disease (gene model comparison: G *vs.* A).