Association of *BDNF* and *BCHE* with Alzheimer's disease: Meta-analysis based on 56 genetic case-control studies of 12,563 cases and 12,622 controls

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Abstract. Alzheimer's disease (AD) is a common neurodegenerative disorder that can destroy the memory of sufferers and lead to distress for the individual and society. Brain-derived neurotrophic factor (*BDNF*) and butyrylcholinesterase (*BCHE*) are two genes associated with β-amyloid plaques and neurofibrillary tangles that are two key factors in the pathophysiology of AD. The aim of the current meta-analysis was to evaluate the association between *BDNF* Val66Met (rs6265), *BDNF* C270T (rs2030324) and *BCHE*-K (rs1803274) polymorphisms and AD. A comprehensive meta-analysis was performed using the online database PubMed without a time limitation. A total of 56 articles evaluating 12,563 cases and 12,622 controls were selected for the current meta-analysis. The results showed a moderate association of the *BDNF* C270T polymorphism with the risk of AD in Asians under a dominant model (P=0.03; odds ratio, 1.88; 95% confidence interval, 1.08-3.27). No other significant association was found during the meta-analysis for the other two polymorphisms (P>0.05). The current meta-analysis suggests that *BDNF* C270T is a risk factor for AD in Asians. This meta-analysis has been, to the best of our knowledge, the most comprehensive meta-analysis of *BDNF* Val66Met, *BDNF* C270T and *BCHE*-K to date.

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Introduction

Alzheimer's disease (AD) is a common neurodegenerative disorder that is the main cause of dementia. The clinical presentation of AD is characterized by progressive memory disorder and cognitive dysfunction (1). The worldwide prevalence of AD was 26.6 million in 2006, and this number is predicted to quadruple by 2050. The rapidly increased AD incidence is likely lead to a significant burden on family and society (2).

AD is a complex disease involving the interaction of genetic and environmental factors. It has been shown that AD development is contributed to by several elements, such as senile plaques, neurofibrillary tangles (NFTs), abnormally aggregated 'reactive' proteins like β-amyloid (Aβ) and tau, exposure to aluminum and brain inflammation (3). A genome-wide association study revealed that multiple mutations in candidate genes greatly increase the chance of developing AD (4). Genes such as brain-derived neurotrophic factor (*BDNF*) and butyrylcholinesterase (*BCHE*) are believed to play a significant role in AD progression (5-7).

BDNF is a member of the neurotrophic factor family and is encoded by a gene located on chromosome 11p13 (8). A previous study demonstrated that the levels of BDNF and its receptor, tyrosine receptor kinase B, were decreased in the frontal cortex and hippocampus of patients with AD (9). BDNF is known to protect against the neurotoxicity of the Aβ peptide and neural cell death by the aggregation of Aβ and tau proteins (10,11). Several single nucleotide polymorphisms (SNPs), such as Val66Met and C270T (rs2030324), in *BDNF* have been reported to be associated with AD (12-19).

BCHE is located on chromosome 3q26 (20), spanning over 73 kb with four exons and three large introns (21). The protein, BCHE, is an acetylcholine-hydrolyzing enzyme. *BCHE* is considered to be relevant to the progressive memory disorder

and dementia in AD (22,23) and has been associated with NFTs and Aβ in the pathology of AD (24). In addition, *BCHE* has been found to play an important role in AD plaque maturation (25).

Inconsistent results have been reported in the previous studies on the association of *BDNF* and *BCHE* polymorphisms with AD. For *BDNF* Val66Met, there have been five positive results in Europeans (12-15) and Asians (16), and 21 negative results (among 18 studies) in Europeans (26-37), Asians (19,38-42) and Africans (29). For *BDNF* C270T, there have been four positive results in Europeans (13,17) and Asians (18,19) and 14 negative results in Europeans (28-31,34-37,43-45), Asians (40,41) and Africans (29). For *BCHE*-K variants, there have been six positive results in Europeans (46-51) and 22 negative results in Europeans (5,52-67) and Asians (68-72). Discrepancies among the previous association studies may have been the result of limited power, different ethnic backgrounds or the different processes and status in patients with AD. Meta-analysis can strengthen the power by combining data from different studies and can draw a more comprehensive conclusion by analyzing studies in different ethnicities (73-75). The aim of the current meta-analysis was to assess the association between the three polymorphisms and AD.

Materials and methods

Article retrieval. Articles were retrieved in January 2014 by searching PubMed without time or language restrictions. The following keywords were used: 'Alzheimer disease BCHE association or Alzheimer disease BCHE polymorphism' and 'Alzheimer disease BDNF association or Alzheimer disease BDNF polymorphism'. The current meta-analysis included studies that met the following criteria: i) An original case-control study assessing the association of *BDNF* and *BDHE* with AD in humans; ii) a study containing sufficient information for the odds ratios (ORs) and 95% confidence intervals (CIs) to be obtained; iii) a study in which the genotype distribution of each polymorphism in controls met the Hardy-Weinberg equilibrium (HWE); iv) a study in the cumulative number of stages for one genetic locus was at least three. From each study, the following data were extracted or calculated: First author, publication year, country, ethnicity, number of cases and controls, HWE for controls, reported association results and the power of each study.

Data analysis. Arlequin software (76) was used to test whether the genotyping distribution in the controls was in HWE. The power of each study was calculated by a Power and Sample Size Calculation program (77). Cochran's Q statistic and I^2 test (78) were used to evaluate the statistical heterogeneity. A fixed-effect model was used for the studies with minimal to moderate heterogeneity (I^2<50%), and the random-effect model was used for the studies with significant heterogeneity (I^2≥50%), with the exception of the allelic analysis. Subgroup analyses were performed in different inheritable models that contained dominant, recessive and additive models. Review Manager 5 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) was used to estimate the combined ORs and CIs (79). Funnel plots were drawn to observe the potential publication bias. P<0.05 was considered to indicate a statistically significant difference.

Results

Article retrieval. As shown in Fig. 1, 104 articles were obtained from the two searches. Two non-human studies were excluded, as were five non-AD studies, three reviews, 35 studies that only focused on patients and nine case-control studies without genotyping information. In addition, six studies were included from the references. The genotypes in the controls of the case-control studies met the HWE. Finally, 56 articles (5,12-19,26-72) with 12,563 cases and 12,622 controls among 72 stages were involved in the present meta-analysis. The characteristics of the included studies are shown in Table I.

BDNF Val66Met. A total of 23 articles with 26 stages involving 6,504 patients with AD and 6,636 controls were included for the meta-analysis of *BDNF* Val66Met. Significant statistical heterogeneity was found at the allelic level (I^2=58%), under the dominant model (I^2=56%) and the additive model (I^2=53%). The major allele frequency of *BDNF* Val66Met was 0.805 in Europeans [International Haplotype Mapping Project panel derived from Utah residents with Northern and Western European ancestry (HapMap-CEU)], higher than the frequency in Asians [HapMap-Han Chinese in Beijing, China (HCB), 0.733; HapMap-Japanese in Tokyo Japan (JPT), 0.682] and Africans [HapMap-Yoruba in Ibadan, Nigeria (YRI), 0.004]. The ethnic differences for *BDNF* Val66Met were low between different populations [Fixation index (F_{st})=0.1006]; therefore, the meta-analysis was also performed by ethnicity. No significant association was found in the meta-analysis on allelic analysis (P=0.99; OR, 1.00; 95% CI, 0.91-1.10; Table II) or under the other models for combined and stratified populations (P>0.05, Table II).

BDNF C270T. A total of 17 articles with 18 stages involving 4,216 patients with AD and 4,370 controls were included for the meta-analysis of the *BDNF* C270T polymorphism. Significant heterogeneity was observed in the meta-analysis at the allelic level (I^2=63%) and under the dominant model (I^2=62%). The frequency of the *BDNF* C270T allele was 0.667 in Chinese subjects (HapMap-HCB), higher than that in the Japanese group (HapMap-JPT, 0.455), Europeans (HapMap-CEU, 0.570) and Africans (HapMap-YRI, 0.550). Further analysis showed a low ethnic difference for *BDNF* C270T (F_{st}=0.0230). No significant association between *BDNF* C270T and AD was observed at the allelic level (P=0.30; OR, 1.12; 95% CI, 0.91-1.37; Table II). A further subgroup meta-analysis by ethnicity showed a significant association between *BDNF* C270T and AD in Asians under a dominant model (P=0.03; OR, 1.88; 95% CI, 1.08-3.27; Table II and Fig. 2).

BCHE-K. A total of 28 articles with 4,894 patients with AD and 4,367 controls were included for the meta-analysis of the *BCHE*-K variant. Although minimal ethnic differences were found in Europeans and Asians (F_{st}=0.0009), significant heterogeneity was found in the meta-analysis on the allelic level (I^2=56%) and under the dominant model (I^2=65%); however, no significant association was found at the allelic level (P=0.31; OR, 1.07; 95% CI, 0.94-1.21; Table II). Subgroup meta-analysis also did not yield any significant results (P>0.05, Table II).

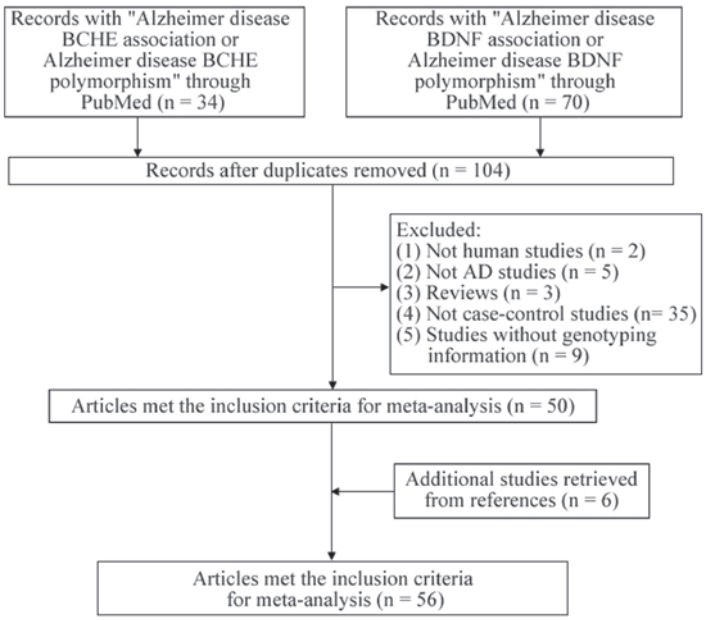

Figure 1. Flowchart of the selection process in the meta-analysis. AD, Alzheimer's disease; BCHE, butyrylcholinesterase; BDNF, brain-derived neurotrophic factor.

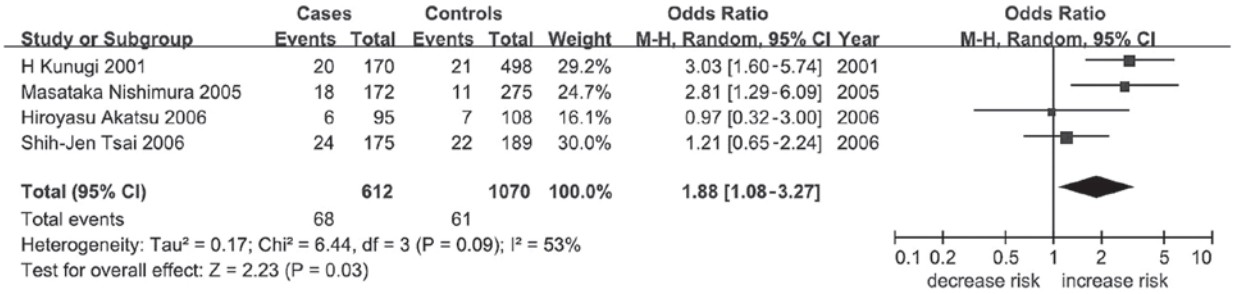

Figure 2. Forest plot of the association of the brain-derived neurotrophic factor C270T polymorphism with Alzheimer's disease in Asians. M-H, Mantel-Haenszel; CI, confidence interval.

Power analyses. The power analyses in this meta-analysis were calculated under a moderate risk of AD (OR, 1.2; Tables I and II). The power was 1.000 for *BDNF* Val66Met, 0.986 for *BDNF* C270T and 1.000 for the *BCHE*-K variant (Table II), which was considerably higher than that in each of the individual studies (Table I). No publication bias was found in the meta-analyses of the three SNPs (Fig. 3).

Discussion

In the present study, 56 studies (72 stages) among 12,563 cases and 12,622 controls were analyzed to assess the association of the *BDNF* Val66Met, *BDNF* C270T and *BCHE*-K variants with AD. The results showed a moderate association between *BDNF* C270T and AD in Asians (P=0.03; OR, 1.88; 95% CI, 1.08-3.27; Table II and Fig. 2) but no significant associations were observed in the other meta-analyses.

The *BDNF* Val66Met polymorphism has been shown to impair the secretion of BDNF (80), and to be able to change brain morphology and cognitive function (81). Previous studies have reported five positive results (12-16) and 21 negative results (19,26-42) between the *BDNF* Val66Met polymorphism and AD. In the present meta-analysis, no significant association was found between *BDNF* Val66Met and AD (P>0.05, Table II). This was consistent with a former meta-analysis (82). The current meta-analysis of *BDNF* Val66Met included 23 articles, seven more than the previous study. In addition, meta-analyses were performed under various genetic models, including dominant, recessive and additive models. Subgroup meta-analysis by ethnicity was also conducted, although no statistically significant results were obtained.

The *BDNF* C270T polymorphism is located in a non-coding region and may affect the *BDNF* expression in the neural soma, dendrites or axonal regions (83). Heterozygous carriers of the T-allele tend to have a higher risk of developing AD than non-carriers (36). There have been a total of four significant results (13,17-19) and 14 non-significant results (28-31,34-37,40,41,43-45) among the previous association studies between the *BDNF* C270T polymorphism and AD. In the present meta-analysis, the *BDNF* C270T polymorphism was found to increase the risk of AD by 88% in Asians under the dominant model. No significant association was found in the other analyses (P>0.05, Table II). A strong power was shown in the meta-analysis of *BDNF* C270T polymorphism

Table I. Characteristics of the case-control studies in the current meta-analysis.

First author (ref)	Year	Country	Ethnicity	Cases/controls (n/n)	HWE	Result	Power
BDNF Val66Met							
Ventriglia (12)	2002	Italy	Europeans	130/111	Yes	S	0.052
Saarela (13)	2006	Finland	Europeans	97/101	Yes	S	0.086
Nacmias (26)	2004	Italy	Europeans	83/97	Yes	NS	0.117
Combarros (27)	2004	Spain	Europeans	237/218	Yes	NS	0.197
Tsai (38)	2004	China	Asians	163/89	Yes	NS	0.164
Bian (39)	2005	China	Asians	203/239	Yes	NS	0.266
Lee (28)	2005	USA	Europeans	95/70	Yes	NS	0.119
Nishimura (19)	2005	Japan	Asians	172/275	Yes	NS	0.262
Desai 1 (29)	2005	USA[a]	Europeans	995/671	Yes	NS	0.516
Desai 2 (29)	2005	USA[b]	Africans	64/45	Yes	NS	0.054
Matsushita (16)	2005	Japan	Asians	487/471	Yes	S	0.512
Vepsäläinen (30)	2005	Finland	Europeans	375/460	NA	NS	0.254
Bodner (31)	2005	USA	Europeans	256/194	Yes	NS	0.192
Li 1 (32)	2005	UK	Europeans	359/396	Yes	NS	0.285
Li 2 (32)	2005	USA[c]	Europeans	188/361	Yes	NS	0.222
Li 3 (32)	2005	USA[d]	Europeans	388/349	Yes	NS	0.271
Forero (33)	2006	Colombia	Europeans	101/168	Yes	NS	0.111
Akatsu (40)	2006	Japan	Asians	95/108	Yes	NS	0.146
Zhang (34)	2006	USA	Europeans	295/250	Yes	NS	0.224
Tsai (41)	2006	China	Asians	175/189	Yes	NS	0.229
Huang (35)	2007	USA	Europeans	220/128	Yes	NS	0.124
He (42)	2007	China	Asians	513/575	Yes	NS	0.564
Cozza (37)	2008	Italy	Europeans	251/97	Yes	NS	0.139
Feher (14)	2009	Hungary	Europeans	160/164	Yes	S	0.211
Pivac (15)	2011	Croatia	Europeans	211/402	Yes	S	0.235
Boiocchi (36)	2013	Italy	Europeans	191/408	Yes	NS	0.262
BDNF C270T							
Kunugi (18)	2001	Japan	Asians	170/498	Yes	S	0.084
Riemenschneider (43)	2002	Germany	Europeans	210/188	Yes	NS	0.076
Nishimura (44)	2004	Brazil	Europeans	188/188	Yes	NS	0.088
Olin (17)	2005	US	Europeans	212/202	Yes	S	0.076
Lee (28)	2005	USA	Europeans	106/73	Yes	NS	0.063
Nishimura (19)	2005	Japan	Asians	172/275	Yes	S	0.073
Desai 1 (29)	2005	USA[a]	Europeans	719/523	Yes	NS	0.207
Desai 2 (29)	2005	USA[b]	Africans	58/42	Yes	NS	0.056
Vepsäläinen (30)	2005	Finland	Europeans	375/460	Yes	NS	0.457
Bodner (31)	2005	USA	Europeans	256/194	Yes	NS	0.088
Akatsu (40)	2006	Japan	Asians	95/108	Yes	NS	0.065
Zhang (34)	2006	USA	Europeans	295/250	Yes	NS	0.113
Saarela (13)	2006	Finland	Europeans	97/101	Yes	S	0.089
Tsai (41)	2006	China	Asians	175/189	Yes	NS	0.096
Huang (35)	2007	USA	Europeans	220/128	Yes	NS	0.081
Cozza (37)	2008	Italy	Europeans	251/97	Yes	NS	0.091
Cousin (45)	2011	France	Europeans	425/470	Yes	NS	0.152
Boiocchi (36)	2013	Italy	Europeans	192/384	Yes	NS	0.308
BCHE-K							
Lehmann (51)	1997	UK	Europeans	74/104	NA	S	0.083
Singleton (63)	1998	UK	Europeans	119/83	Yes	NS	0.111
Crawford (62)	1998	USA	Europeans	391/201	Yes	NS	0.182
Brindle (64)	1998	USA	Europeans	188/165	NA	NS	0.161
Piccardi (55)	2007	Italy	Europeans	158/118	Yes	NS	0.109

Table I. Continued.

First author (ref)	Year	Country	Ethnicity	Cases/controls (n/n)	HWE	Result	Power
Kehoe (60)	1998	UK	Europeans	181/71	Yes	NS	0.093
Ki (71)	1999	Korea	Asians	78/74	NA	NS	0.231
Wiebusch (50)	1999	Canada	Europeans	135/70	Yes	S	0.094
Grubber (59)	1999	USA	Europeans	245/241	NA	NS	0.137
Tilley (58)	1999	UK	Europeans	177/118	Yes	NS	0.145
McIlroy (49)	2000	Ireland	Europeans	175/187	Yes	S	0.175
Yamamoto (70)	1999	Japan	Asians	203/288	NA	NS	0.087
Lee (69)	2000	China	Asians	89/101	NA	NS	0.086
Mattila (57)	2000	Finland	Europeans	80/67	Yes	NS	0.077
Bi	2001	China	Asians	38/40	Yes	NS	0.171
Prince (56)	2001	Sweden	Europeans	201/166	Yes	NS	0.103
Raygani (47)	2004	Iran	Europeans	105/129	Yes	S	0.146
Combarros (46)	2005	Spain	Europeans	187/172	Yes	S	0.134
Deniz-Naranjo (54)	2007	Spain	Europeans	282/312	Yes	NS	0.248
Mateo (53)	2008	Spain	Europeans	231/221	Yes	NS	0.144
Scacchi (5)	2009	Italy	Europeans	471/254	Yes	NS	0.279
Simão-Silva	2013	Brazil	Europeans	78/80	Yes	NS	0.108
Russ (65)	1998	UK	Europeans	203/122	NA	NS	0.100
Hiltunen (61)	1998	Finland	Europeans	59/59	Yes	NS	0.090
Yamada (72)	1998	Japan	Asians	48/107	Yes	NS	0.096
Alvarez-Arcaya (48)	2000	Spain	Europeans	202/249	NA	S	0.141
Helbecque (66)	1998	Various[e]	Europeans	336/344	Yes	NS	0.272
Laws (67)	1999	Australia	Europeans	237/348	NA	NS	0.239

[a]Caucasian descent; [b]African-American. [c]Samples collected from the University of California, San Diego, CA, USA; [d]samples collected from Washington University Alzheimer's Disease Research Center patient registry (Seattle, WA, USA). [e]France, UK, Spain, Italy and the Netherlands. HWE, Hardy-Weinberg equilibrium; NS, not significant; S, significant; NA, not applicable; *BDNF*, brain-derived neurotrophic factor; *BCHE*, butyrylcholinesterase.

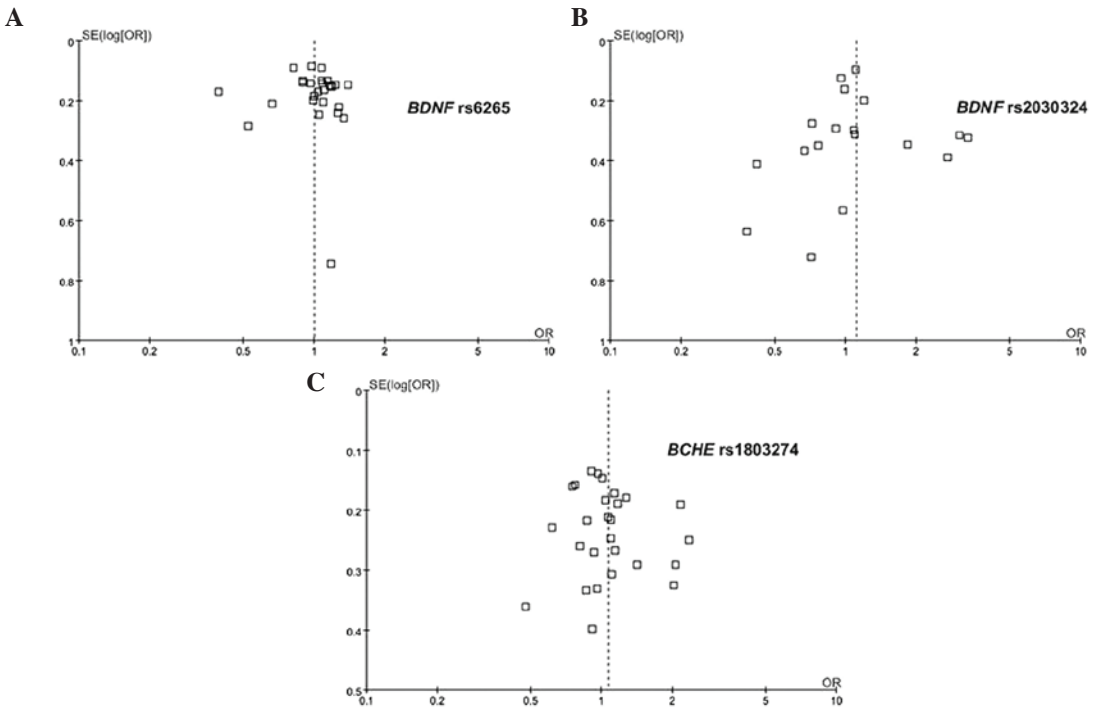

Figure 3. Funnel plots of the association of the (A) *BDNF* Val66Met, (B) *BDNF* C270T and (C) *BCHE*-K polymorphisms with Alzheimer's disease. *BDNF*, brain-derived neurotrophic factor; *BCHE*, butyrylcholinesterase; SE, standard error; OR, odds ratio.

Table II. Meta-analysis of the association of the *BDNF* Val66Met, *BDNF* C270T and *BCHE*-K polymorphisms with Alzheimer's disease.

A, *BDNF* Val66Met polymorphism

Genetic model	Cases/controls (n/n)	Ethnicity	No. of studies	OR (95% CI)	P-value	I^2 (%)	Power
Overall (M vs. V)	6504/6636	Overall	26	1.00 (0.91-1.10)	0.99	58	1.000
	4632/4645	Europeans	18	1.01 (0.88-1.15)	0.89	65	0.999
	1808/1946	Asians	7	0.95 (0.87-1.04)	0.26	38	0.976
	64/45	Africans	1	1.18 (0.27-5.06)	0.82	NA	0.054
Dominant (MM/MV vs. VV)	6129/5982	Overall	25	1.03 (0.90-1.18)	0.65	56	1.000
	4257/4185	Europeans	17	1.03 (0.87-1.22)	0.72	64	1.000
	1808/1946	Asians	7	0.98 (0.85-1.13)	0.82	16	0.938
	64/45	Africans	1	1.19 (0.27-5.24)	0.82	NA	0.060
Recessive (MM vs. MV/VV)	6129/6176	Overall	25	0.90 (0.80-1.02)	0.43	42	0.997
	4257/4185	Europeans	17	0.95 (0.78-1.15)	0.58	44	0.880
	1808/1946	Asians	7	0.87 (0.74-1.02)	0.09	44	0.918
	64/45	Africans	1	NA	NA	NA	NA
Additive (MM vs. VV)	3650/3753	Overall	25	0.92 (0.71-1.18)	0.50	53	0.988
	2160/2419	Europeans	17	0.82 (0.57-1.18)	0.28	59	0.934
	1393/1271	Asians	7	1.11 (0.85-1.45)	0.43	9	0.631
	97/63	Africans	1	0.85 (0.33-2.15)	0.73	NA	0.085

B, *BDNF* C270T polymorphism

Genetic model	Cases/controls (n/n)	Ethnicity	No. of studies	OR (95% CI)	P-value	I^2 (%)	Power
Overall (T vs. C)	4216/4370	Overall	18	1.12 (0.91-1.37)	0.30	63	0.986
	3546/3258	Europeans	13	1.01 (0.83-1.24)	0.92	58	0.982
	612/1070	Asians	4	1.80 (0.99-3.27)	0.06	62	0.154
	58/42	Africans	1	0.71 (0.17-2.94)	0.64	NA	0.056
Dominant (TT/TC vs. CC)	4216/4370	Overall	18	1.10 (0.87-1.39)	0.40	62	0.999
	3546/3258	Europeans	13	0.99 (0.78-1.25)	0.91	58	0.998
	612/1070	Asians	4	1.88 (1.08-3.27)	0.03[a,b]	53	0.241
	58/42	Africans	1	0.70 (0.17-2.99)	0.63	NA	0.064
Recessive (TT vs. TC/CC)	4216/4370	Overall	18	1.12 (0.88-1.42)	0.37	0	0.725
	3546/3258	Europeans	13	1.12 (0.88-1.43)	0.37	0	0.737
	612/1070	Asians	4	1.33 (0.03-51.71)	0.88	64	0.062
	58/42	Africans	1	NA	NA	NA	NA

Table II. Continued.

Genetic model	Cases/controls (n/n)	Ethnicity	No. of studies	OR (95% CI)	P-value	I^2 (%)	Power
Additive (TT vs. CC)	3528/3609	Overall	18	1.17 (0.88-1.54)	0.29	0	0.722
	2929/2560	Europeans	13	1.17 (0.88-1.55)	0.29	0	0.738
	545/1011	Asians	4	1.40 (0.03-57.09)	0.86	64	0.063
	54/38	Africans	1	NA	NA	NA	NA

C, *BCHE*-K polymorphism

Genetic model	Cases/controls (n/n)	Ethnicity	No. of studies	OR (95% CI)	P-value	I^2 (%)	Power
Overall (K vs. W)	4769/4242	Overall	27	1.07 (0.94-1.21)	0.31	56	1.000
	4313/3632	Europeans	22	1.06 (0.92-1.22)	0.45	63	0.994
	456/610	Asians	5	1.17 (0.92-1.47)	0.20	0	0.341
Dominant (KK/KW vs. WW)	3659/2992	Overall	20	1.01 (0.84-1.22)	0.89	65	0.999
	3573/2845	Europeans	18	1.02 (0.83-1.24)	0.88	69	0.998
	86/147	Asians	2	0.97 (0.55-1.73)	0.93	0	0.151
Recessive (KK vs. KW/WW)	3452/2628	Overall	19	1.15 (0.85-1.54)	0.36	0	0.455
	3366/2481	Europeans	17	1.19 (0.88-1.61)	0.25	0	0.433
	86/147	Asians	2	0.35 (0.05-2.22)	0.26	0	0.073
Additive (KK vs. WW)	2430/1995	Overall	19	1.19 (0.90-1.58)	0.23	0	0.439
	2372/1891	Europeans	17	1.23 (0.92-1.65)	0.15	0	0.418
	58/104	Asians	2	0.36 (0.06-2.29)	0.28	0	0.073

[a]P≤0.05; [b]significance of P-value lost following correction by multiple testing. *BDNF*, brain-derived neurotrophic factor; *BCHE*, butyrylcholinesterase; NA, not applicable; OR, odds ratio; CI, confidence interval.

(0.986). Compared with a former meta-analysis that showed no positive results (82), the current meta-analysis of *BDNF* C270T included 18 studies, more than the 12 in the previous study (82); the meta-analyses were performed under various genetic models, and subgroup meta-analyses by ethnicity were also conducted. With a larger sample size and more comprehensive analysis, the present study showed a more reliable conclusion than the previous study.

The K variant alone does not decrease *BCHE* activity, but acts in synergy with *APOE4* polymorphism to increase the risk of AD (84). Additionally, the *BCHE*-K variant promotes fibril formation by participating in the transformation of Aβ from an initially benign form to an eventually malignant form. The *BCHE*-K variant acts as a general candidate risk factor of AD (84,85). Six significant results (46-51) and 22 non-significant results (5,52-72) were found in previous studies on the association between the *BCHE*-K variant and AD. The power of *BCHE*-K was 1.000, which was sufficiently strong for a precise conclusion to be drawn. The current study showed no significant association between the *BCHE-K* variant and AD; this was consistent with a previous meta-analysis (86). The present study involved 27 stages, six more than the former study. The studies involved in the present meta-analysis met the HWE and were performed under various genetic models with subgroup meta-analysis by ethnicity. With stricter inclusion criteria, a stronger power and more comprehensive analysis, the present meta-analysis of *BCHE*-K was an improvement on the former one.

There were certain limitations in the meta-analysis. Firstly, publication bias may exist, as the negative-result studies are less likely to be published and may be missed, which may influence the results. Secondly, the majority of studies investigating the association between the three polymorphisms and AD were carried out in the European and Asian populations. The number of studies in other populations, such as Africans, was limited. Future studies in other ethnic populations are warranted. Thirdly, AD is a complex disease. Different statuses in AD may affect the results of the study; however, no detailed information of the AD diagnostic criteria was available from previous studies. Future case-control studies with more comprehensive information are required. Fourthly, there are 5,724 polymorphisms in *BDNF* and 5,059 polymorphisms in *BCHE*. The current study only focused on two polymorphisms of *BDNF* and one polymorphism of *BCHE*, which may not fully show the function of those two genes. Studies investigating a wider range of polymorphisms are required to improve the representation of the two genes. Fifthly, *APOE* is a known pivotal gene in the AD pathogenesis but no *APOE* genotype was included in any of the studies. Thus, any hidden interaction of the *APOE* genotype with the tested three polymorphisms may have been missed in the current meta-analysis. Sixthly, although a moderate association of the *BDNF* C270T polymorphism with the risk of AD was observed in Asians under a dominant model (P=0.03; OR, 1.88; 95% CI, 1.08-3.27), the significance was not retained following correction by multiple testing. This result should therefore be taken with caution. Finally, there was high heterogeneity in the *BDNF* C270T variant under the dominant model in Asians (P=0.03, I^2=53%, Table II). We speculated that the number of participants was the source of the heterogeneity, as the studies with limited samples tended to produce negative results (n<200, P>0.05) in contrast to significant results produced in the studies with sufficient samples (n>200, P<0.05).

In conclusion, the present comprehensive meta-analysis suggested a moderate association between the *BDNF* C270T polymorphism and AD in Asians under the dominant model. Further studies focusing on a wider range of ethnic populations are required to confirm the results of the study.

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