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The Brain-Derived Neurotrophic-Factor (*BDNF*) Val66Met Polymorphism Is Associated With Geriatric Depression: A Meta-Analysis

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Abstract

Depression has been associated with reduced expression of brain-derived neurotrophic factor (*BDNF*) in the hippocampus. Genetic association studies of the *BDNF* Val66Met polymorphism (rs6265) in geriatric depression have produced inconsistent results. A meta-analysis of studies was conducted to compare the frequency of the *BDNF* Val66Met variant between cases with geriatric depression and age-matched controls. A total of five studies involving 523 cases with geriatric depression and 1,220 psychiatrically healthy controls was included. Met allele carriers had an increased risk for geriatric depression when compared to Val/Val homozygotes (P =0.004, OR =1.48, 95% CI =1.13–1.93). Our findings suggest the *BDNF* Met allele may confer increased risk for depression as individual age.

Keywords

BDNF; Val66Met; geriatric; depression; meta-analysis

INTRODUCTION

Depression among the elderly (geriatric depression) is a common psychiatric condition, with a prevalence of 10–20% [Borson et al., 1986; Beekman et al., 1995; Copeland et al., 1999]. Geriatric depression is associated with personal suffering as well as elevated risk of mortality due to suicide and medical illness; it is also associated with increased disability associated with medical and cognitive disorders [Lebowitz et al., 1997; Alexopoulos and Kelly, 2009].

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The causes of geriatric depression are likely diverse and complex, and heritable factors contribute to the disorder [Alexopoulos and Kelly, 2009]. Studies to date have moved the field of mood disorders research beyond the monoamine hypothesis of depression. Neurotrophic factors in limbic brain regions play an important role in the regulation of mood and cognition. Brain-derived neurotrophic factor (BDNF) is widely distributed in the central nervous system (CNS), including the hippocampus, neocortex, amygdala, cerebellum, and hypothalamus, all of which are key regions in the regulation of mood. BDNF is necessary for dendritic growth, synaptic plasticity, and long-term potentiation [Maisonpierre et al., 1990]. Additionally, it modulates the activity of neurotransmitter systems in the CNS involved in many mood disorders including serotonin, dopamine, and glutamate [Mossner et al., 2000; Guillin et al., 2001; Carvalho et al., 2008]. Hippocampal BDNF levels decrease in depression and increase following anti-depressant treatment [Kuroda and McEwen, 1998; Madsen et al., 2000; Chen et al., 2001; Dranovsky and Hen, 2006; Duman and Monteggia, 2006]. Similarly, serum BDNF levels decrease in adult patients with major depression disorder and increase in patients treated with antidepressants [Karege et al., 2002; Castren et al., 2007; Post, 2007; Yoshimura et al., 2007; Piccinni et al., 2008; Sen et al., 2008; Hashimoto, 2010]. One study [Diniz et al., 2010] also found that serum BDNF level is reduced in antidepressant-free patients with late-life depression.

Basic and clinical studies have examined the association between *BDNF* polymorphisms and depression, including geriatric depression. To date, most published studies have focused on a functional valine-to-methionine polymorphism at codon 66 (Val66Met also known as G196A or rs6265) that results from a guanine to adenine substitution at base 196 [Schumacher et al., 2005]. Many studies have shown that the *BDNF* valine-to-methonine substitution at codon 66 produces functional differences [Hariri et al., 2003; Egan et al., 2003a,b; Rybakowski et al., 2003, 2006; Chen et al., 2005, 2006; Dempster et al., 2005; Tan et al., 2005]. In cultured hippocampal neurons, the *Met* allele was associated with differing activity-dependent secretion of the BDNF protein and failure of the protein to localize to secretory granules or synapses [Egan et al., 2003a,b; Chen et al., 2004]. These trafficking abnormalities are likely to reflect impaired binding of the Met allele to sortilin, a Vps10p domain protein that influences sorting of BDNF into regulated secretory pathways [Chen et al., 2005].

Association studies examining the role of the *BDNF* Val66Met polymorphism and geriatric depression have been inconsistent, potentially due to low power in individual studies, etiological heterogeneity, or because of random error in the absence of a true effect [Glatt et al., 2003; Lau and Eley, 2010]. In this study, we carefully reviewed and selected qualified studies, using a meta-analysis to investigate the role of the *BDNF* Val66Met polymorphism in geriatric depression. Meta-analysis provides the most accurate estimate of the nature and magnitude of an effect by combining the results of multiple independent studies, to reduce the potential influence of types I and II errors that occur within individual studies [Gu et al., 2001].

MATERIALS AND METHODS

Search Strategy

All published studies examining the association of the *BDNF* Val66Met polymorphism with geriatric depression were carefully selected by three independent authors (Y.J. Wang, Y. Pei, and W.G. Pan. Data were collected from the electronic databases PubMed and Ovid. These databases were searched from the first date available up to September 30, 2011. The keywords “BDNF”, “brain-derived neurotrophic factor,” “Val66Met,” “rs6265,” “G196A,” “196G/ A,” “mood,” “affective,” “depress,*” “unipolar,” “geriatric,” “old,*” “elder,*” “aged,” and “late onset” were used for searching. Meanwhile, we also searched the reference

lists of included studies to identify other potentially eligible studies. We only included data from full-length papers, not abstracts from conference proceedings.

Inclusion Criteria

All case–control studies reporting genotype or allele frequencies of the Val66Met polymorphisms in geriatric depression and in psychiatrically healthy controls were eligible for inclusion in this meta-analysis. Case status was defined as having a current or 1-year diagnosis of geriatric depression (60 years or older) assessed by established psychiatric interviews. The diagnosis of depression was based on either DSM or ICD, including DSM-III, DSM-III-R, DSM-IV, DSM-IV-R, and ICD-10, or if participants had clinically significant depressive symptoms according to a validated depression rating scale (Table I). We included studies involving samples with any ethnic background. Case-only studies, family-based designs, and population-based studies of healthy subjects were not included. In addition, we did not include studies on post-stroke depression or Alzheimer's disease (AD)-related depression to limit phenotypic heterogeneity.

Data Extraction

Three authors (C.L. Tie, W.G. Pan, and Y. Pei) independently extracted data to avoid potential mistakes. Discrepancies were resolved by discussions within the research team. From each study, we extracted the first author's name, year of publication, source of publication, ethnicity of samples, depression measure (or diagnostic system), number of cases and controls, and the available genotype and allele frequency information of the *BDNF* Val66Met polymorphism. Ethnicity was coded as Caucasian or Asian as determined by the published report. No other ethnicities were involved in the studies included in our analysis.

Meta-Analysis Methods

We examined the relationship between the frequency of the Met allele and diagnosis of geriatric depression. The odds ratio (OR) and its 95% confidence interval (95% CI) were estimated for each study. We performed a chi-squared-based Q-statistic test to assess between-study heterogeneity [Lau et al., 1997]. In this analysis, $P<0.1$ indicates the presence of significant heterogeneity. The inconsistency index I^2 was also calculated to evaluate heterogeneity. We also measured the effect of heterogeneity by another measure, $I^2 = 100\% \times (Q - df)/Q$ [Higgins and Thompson, 2002]. Depending on the results of the heterogeneity tests among individual studies, we used a fixed-effects model (if $P>0.1$) [Mantel and Haenszel, 1959] or a random-effects model (if $P<0.1$) [DerSimonian and Laird, 1986] to summarize the pooled OR. We used a Z-test with a significance threshold of $P<0.05$ to evaluate the OR.

Evaluation of Publication Bias

Publication bias, that is, the preferential publication of a study with positive findings, was evaluated with a funnel plot such that asymmetry of the funnel plot suggests bias. Both Begg's and Egger's tests were used to statistically assess publication bias ($P<0.05$). Sensitivity analysis was conducted by sequential deletion of a single study in an attempt to assess the contribution of each individual dataset to the pooled OR obtained.

All analyses were performed using the software Stata (version 10.1, Stata Corp LP, College Station, TX).

RESULTS

Description of Studies Identified in Meta-Analysis

We identified 20 potentially relevant research papers using our search strategies, but 15 did not meet the inclusion criteria (Fig. 1) after reviewing the abstracts or papers. The excluded papers included five studies that were not focusing on geriatric depression [von Bohlen und Halbach et al., 2006; Hayden et al., 2010; Hedner et al., 2010; Erickson et al., 2011], three review articles [Arantes-Goncalves and Coelho, 2006; Frodl et al., 2008; Savitz and Drevets, 2009], and one that was not a case–control design [Taylor et al., 2011]. We also excluded one study on AD-related depression [Borroni et al., 2009] and two other studies that contained cases or controls younger than 60-year old [Surtees et al., 2007; You et al., 2010], were also excluded. Studies with overlapping patient samples were discarded and the most complete dataset was selected for the meta-analysis [Kim et al., 2008; Lin et al., 2009; Benjamin et al., 2010].

Five case–control datasets were included in this meta-analysis (Table I) [Hwang et al., 2006; Kim et al., 2007; Taylor et al., 2007; Czira et al., 2011; Kanellopoulos et al., 2011]. Overall, the studies included 523 cases and 1,220 psychiatrically healthy controls (3 Caucasians and 2 Asians cohorts).

Effect of *BDNF* Val66Met on Geriatric Depression

We tested the association between geriatric depression and the *BDNF* Val66Met polymorphism by estimating the OR of Met carriers (Met/Met and Val/Met) versus the Val/Val genotype. The pooled analysis was carried out with a fixed-effects model, as no evidence of heterogeneity was found (I^2 =27.3%, P>0.1). The Met allele was significantly associated with geriatric depression (P=0.004, OR =1.48, 95% CI =1.13–1.93). The summary of the meta-analysis for the *BDNF* Val66Met polymorphisms (Met carriers vs. the Val/Val) and geriatric depression is shown in Figure 2.

Publication Bias and Sensitivity Analysis

A funnel plot was generated to explore publication bias, but no evidence asymmetry was observed (Begg's test; Z =0; P=1; Fig. 3). Egger's test was also performed to investigate the symmetry of the funnel plot, and the results were consistent (t = −0.04, P=0.97). Sensitivity analyses were conducted to assess the degree to which each individual study influenced the results of the overall analysis (Fig. 4). If the study with the largest effect size [Taylor et al., 2007] was excluded, the association of the Met allele with geriatric depression would be reduced (P=0.06) in a meta-analysis of the four remaining studies. However, this is consistent with loss of power, and removal of any other study did not significantly impact the results of the overall analysis.

DISCUSSION

To our knowledge, this is the first comprehensive meta-analysis of studies examining the association of the *BDNF* Val66Met polymorphism with geriatric depression. Previously meta-analyses of this polymorphism in adults suggest little, if any, association of this polymorphism with major depressive disorder (MDD) [Chen et al., 2008; Verhagen et al., 2010] or mood disorders [Gratacos et al., 2007].

Our analysis suggests that Met carriers are at increased risk for geriatric depression. The Met allele is associated with decreased activity of the BDNF system [Rybakowski, 2008]. Mice with the *BDNF* Met/Met genotype showed almost a 30% reduction in regulated release of BDNF [Chen et al., 2006]. Further, $BDNF_{Met/Met}$ mice have decreased *N*-methyl-D-aspartic

acid (NMDA) receptor neurotransmission in the CA1 pyramidal neurons as well as decreased NMDA receptor-dependent long-term depression compared to wild-type (*BDNF*$_{Val/Val}$) mice [Ninan et al., 2010]. *BDNF*$_{Met/Met}$ mice also exhibit increased anxiety-related behaviors [Chen et al., 2006] and reduced extinction of fear learning compared with *BDNF*$_{Val/Val}$ mice [Heldt et al., 2007; Soliman et al., 2010].

Decreased activity of the BDNF system resulting from the Met allele may have a greater effect on the elderly. Neuropsychological, neuroimaging, and neuropathological studies support the multi-factorial nature of geriatric depression and delineate it from depression in younger adults [Beekman, 2011]. Studies of geriatric depression show deficits consistent with normal aging as well as cerebrovascular and neurodegenerative disease processes [Smith et al., 2007]. In healthy humans, Met allele carriers have poorer episodic memory performance and reduced hippocampal physiologic engagement during functional magnetic resonance imaging (fMRI) studies; they also have reduced prefrontal and hippocampal gray matter volume [Egan et al., 2003a; Pezawas et al., 2004; Szeszko et al., 2005; Bueller et al., 2006; Yu et al., 2009]. Met carriers also showed a greater age-related decline in hippocampal activation during both encoding and retrieval tasks relative to Val/Val individuals [Sambataro et al., 2010]. Reduced hippocampal volume is also reported in older people with depression, those with both early-onset and late-onset disorders [Hickie et al., 2005]. Patients with late-onset depression also have more white matter hyperintensity than younger adults [Lesser et al., 1996]. In individuals with late-onset depression, the Met66 allele is associated with greater white matter hyperintensity volumes prompting the need to determine how this might be associated with other clinically relevant findings [Taylor et al., 2008]. Above all, we hypothesize that the Met allele might play a more important role in geriatric depression.

A few limitations of this meta-analysis should be acknowledged. First, we did not perform gender-specific analyses because power was limited to detect associations in stratified datasets. Second, we only focused on geriatric depression and excluded studies in which the age of onset was less than or equal to 60 years as well as studies in older adults with AD. Because depression can be a prodromal symptom of AD [Ahmed, 2001], studies in this meta-analysis ruled out possible dementia using the Mini Mental State Examination (MMSE). The relationship between *BDNF* polymorphisms, AD and geriatric depression needs further examination in light of the association between the *BDNF* Met allele and AD [Fukumoto et al., 2010]. Third, studies in this analysis were limited to Caucasians and Asians. As studies in other ethnic groups are conducted, they should be examined in a meta-analytical framework to evaluate the generalizability of these results.

In summary, our analysis suggests that the *BDNF* Met allele is a risk factor for geriatric depression. The differential role of age of onset in the association should be examined in future studies.

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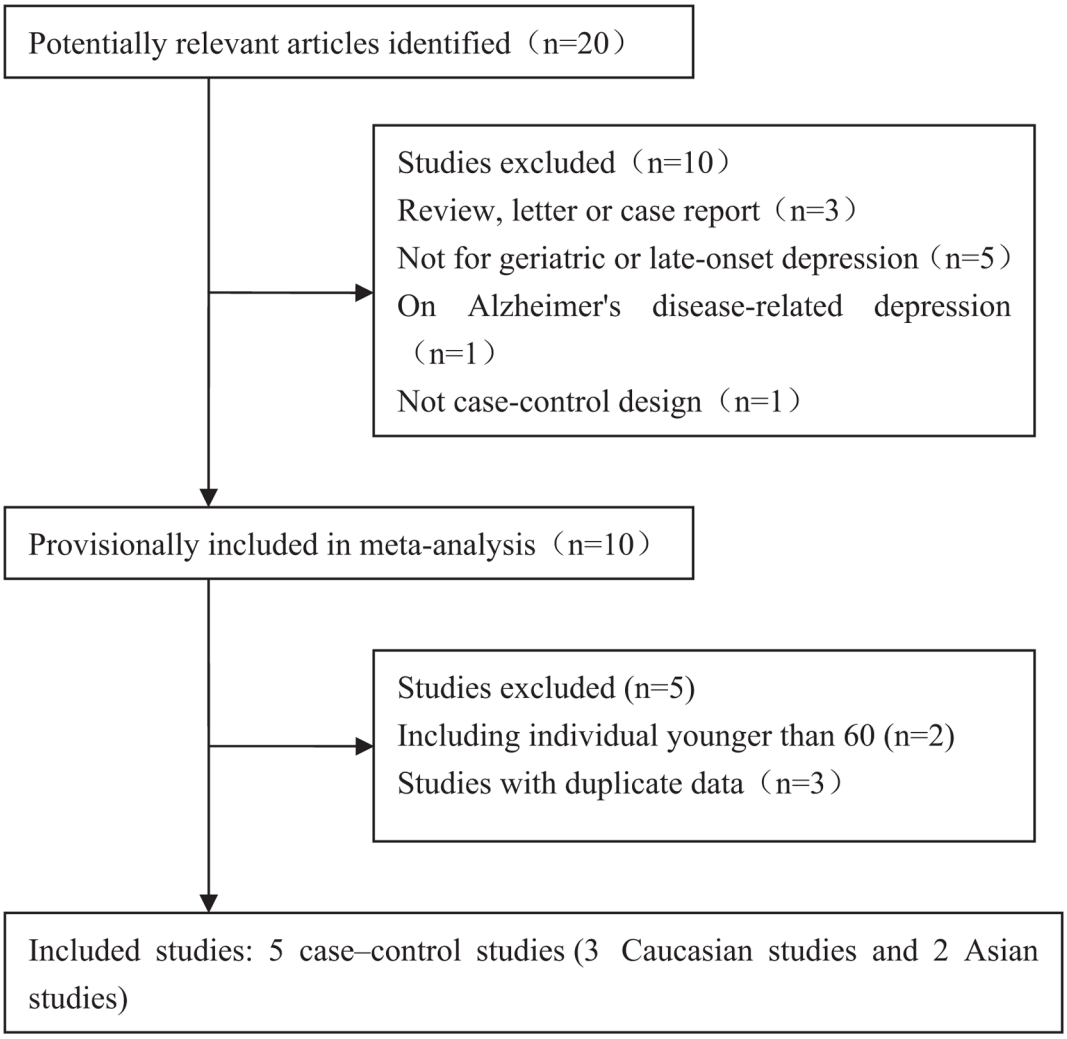

FIG. 1.
Flow diagram of the study selection process. Studies included in this meta-analysis were limited to primary reports of non-overlapping individuals >60-year old with depression. Depression that occurred following a stroke in cohorts with Alzheimer's disease were excluded to limit phenotypic heterogeneity.

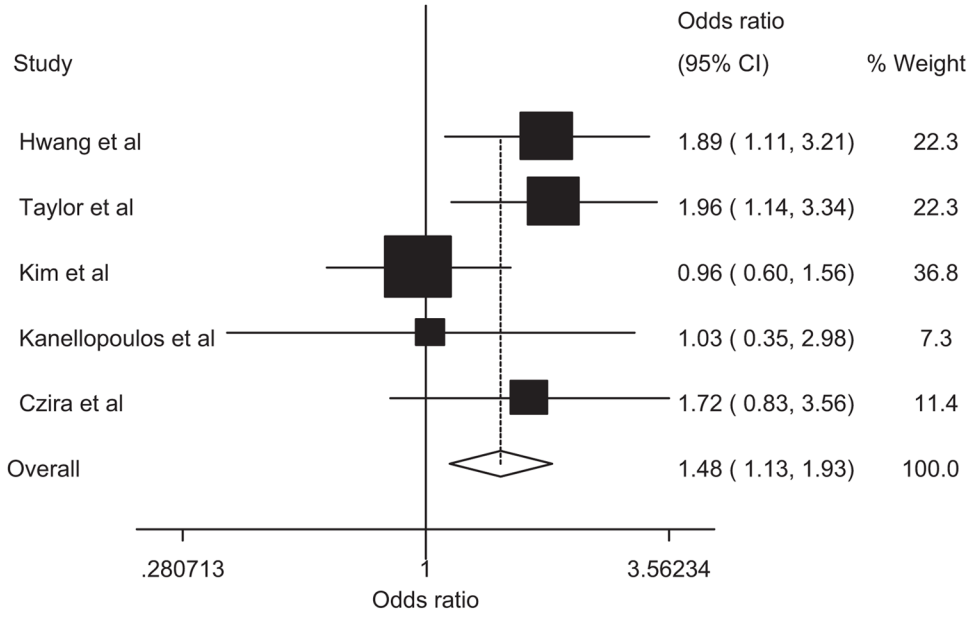

FIG. 2.

Forest plots for meta-analyses. The weight of each study in the overall analysis is reflected by the size of squares. Whiskers represent 95% confidence intervals. The pooled OR for Met carries versus Val/Val is based on the fixed-effect model.

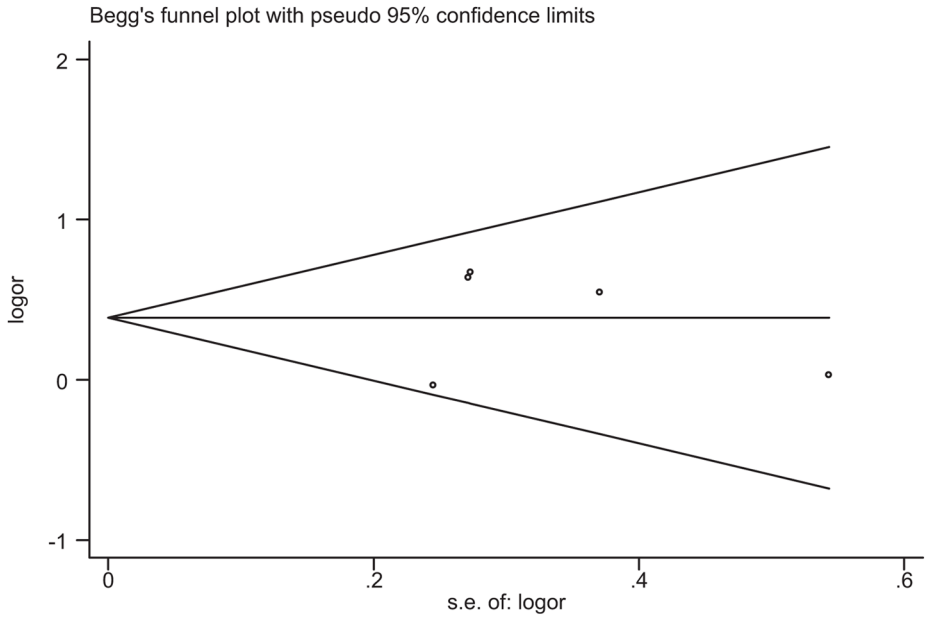

FIG. 3.

Funnel plot analysis to detect publication bias. Each dot represents one study. Location outside the delineated triangle (pseudo 95% confidence intervals) suggests a publication bias.

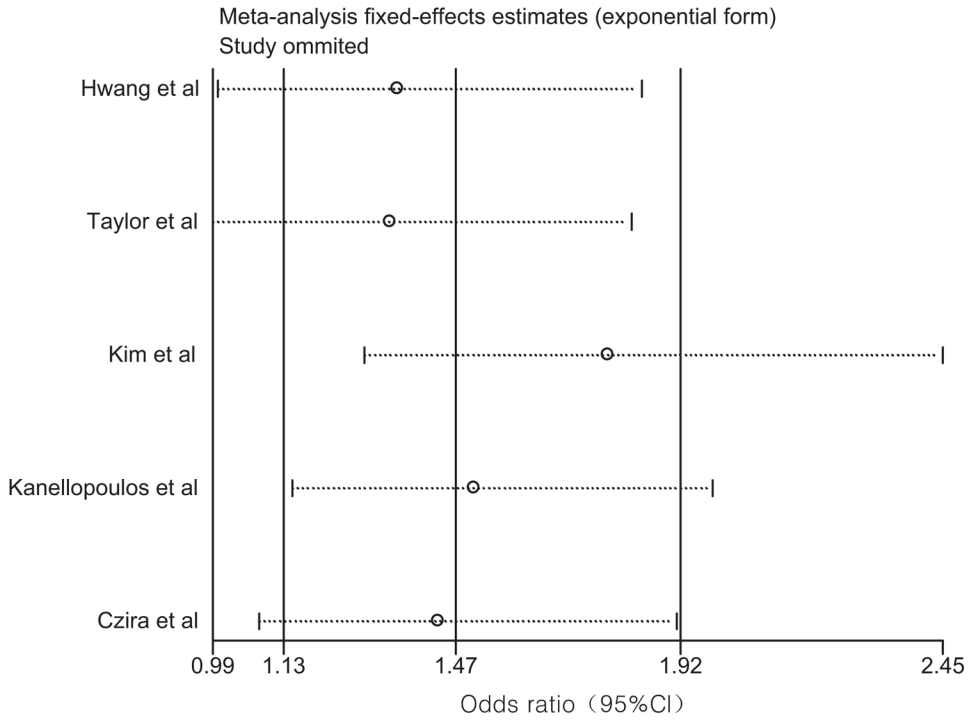

FIG. 4.

Sensitivity of individual studies used in the meta-analysis. The circles represent odds ratio of the overall analyses if the individual study is not included. The lines represent the confidence intervals for the individual study.

TABLE I

Characteristics of the Studies Included in the Meta-Analysis

			Case		Control	
Geriatric disorder Refs.	**Ethnic**	**Depression measure**	**Met carriers**	**Val/Val**	**Met carriers**	**Val/Val**
Hwang et al. [2006]	Asian	DSM-IV	83	27	106	65
Taylor et al. [2007]	Caucasian	DDES	95	150	23	71
Kim et al. [2007]	Asian	GMS	75	26	473	158
Kanellopoulos et al. [2011]	Caucasian	DSM-IV	16	17	11	12
Czira et al. [2011]	Caucasian	CES-D	14	20	87	214
Total			355	344	721	587

Met, methionine; Val, valine; DDES, Duke Depression Evaluation Schedule; GMS, Geriatric Mental State diagnostic schedule; CES-D, Center for Epidemiologic Studies-Depression.