



Association between *FKBP5* polymorphisms and depressive disorders or suicidal behavior: A systematic review and meta-analysis study

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ABSTRACT

Psychiatric disorders are complex polygenic diseases that show common genetic vulnerability. Several studies have investigated the association of polymorphisms of FK506 binding protein 51 (FKBP5) gene and depressive disorders or suicidal behavior, however, the results have been controversial and ambiguous. The aim of our study was to explore the role of the *FKBP5* gene variants (rs1360780, rs3800373 and rs4713916), in depressive disorders or suicidal behavior through a systematic review and a meta-analysis. The protocol number of the study is PROSPERO CRD42018089295. The meta-analysis included 12 studies. Odds ratios with 95% confidence intervals were used to evaluate the association and the publication bias was tested by Egger's test and funnel plot; heterogeneity was assessed by the Cochran's chi-square-based Q statistic test and the inconsistency index. Our results showed that the rs3800373 and rs4713916 were associated with an increased risk of depressive disorders when using the heterozygous and dominant models. In the stratified analysis by ethnicity, a significantly increased risk of depressive disorders was also observed for rs3800373 and rs4713916 in Caucasians. When we analyzed suicidal behavior, we found a significant association with the rs1360780 of *FKBP5* and suicidal behavior risk in the overall population and rs3800373 in completed suicide subgroup. Existing evidence indicates that the polymorphisms of *FKBP5* gene are associated with risk of depressive disorders and suicidal behavior. Future studies with larger sample sizes will be necessary to confirm the present results.

1. Introduction

Genetics contribute to the susceptibility of most psychiatric conditions, therefore the study and understanding of genetic factors is rapidly increasing. Depression is a common disabling psychiatric disorder that has serious repercussions for the individual, his/her family, workplace, and society in general. This disease usually appears with typical symptoms, more covertly but often including nervousness, irritability, sleeping problems and decreased energy (Cameron et al., 2014; Criado-Marrero et al., 2018). While suicide behavior is highly prevalent among patients with depression (Ponsoni et al., 2018). Suicide behavior is a general term encompassing any suicidal thought or action (planning or

actions that go from non-fatal attempts to attempts that result in death); highly complex and multifaceted in which the causes are not fully understood. A possible mechanism that has been proposed, is the dysregulated hypothalamic-pituitary-adrenal axis activity (Barzilay and Apter, 2014). Cortisol binding to glucocorticoid receptor (GR) as well as GR sensitivity are inhibited by FK506 binding protein 51 (FKBP51) (Binder, 2009). The FKBP51 interaction with the central chaperone heat shock protein (Hsp) 90, competes with other proteins for access to the Hsp90-GR heterocomplex and interferes with the activity of GR-stimulatory factors (Schulke et al., 2010; Touma et al., 2011).

The *FKBP5* gene which encodes the FK506 binding protein 51, has received increasing attention in relation to suicidal behavior. In

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humans, the *FKBP5* is located on chromosome 6 and participates as regulator of the GR activity (Fries et al., 2017; Zannas and Binder, 2014). The FKBP51 protein is an important modulator of stress response that regulates a multitude of cellular processes in both brain and periphery (Zannas and Binder, 2014; Zannas et al., 2016). Therefore, *FKBP5* single nucleotide polymorphisms (SNPs) have been associated with an increased risk of major depression or depressive symptoms and suicide attempts (Appel et al., 2011; Kohrt et al., 2015; Tozzi et al., 2016; Yeo et al., 2017). The distributions of TT, TC, and GT haplotypes of the *FKBP5* gene (comprised of rs3800373 and rs1360780) have been associated with completed suicide (Supriyanto et al., 2011); moreover, several SNPs have also been associated with functional of the protein (Fudalej et al., 2015; Supriyanto et al., 2011).

Thus, we identified relevant reports describing the involvement of *FKBP5* gene through a systematic search strategy and a meta-analysis, to assess the connection between *FKBP5* and the outcome of individuals with depressive disorders (monopolar, non-psychotic and major depression) or suicidal behavior (suicide attempt, completed suicide and suicide ideation). Given that a variety of *FKBP5* SNPs have been investigated in different studies, we only selected SNPs that were reported in at least 3 studies across depressive disorders or suicidal behavior. As a result, three SNPs were eligible for this meta-analysis: rs1360780, rs3800373 and rs4713916. A total of 12 studies were identified and included in this meta-analysis. For depressive disorders we included nine publications comprising 3955 cases and 5647 controls; whereas for suicidal behavior we included three publications comprising 751 cases and 703 controls. We also conducted subgroup and sensitivity analyses to further ascertain the possible relationship with depressive disorders or suicidal behavior.

2. Methods

2.1. Search approach and study selection

To perform this meta-analysis we followed the guidelines and methods of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher et al., 2009; Welch et al., 2016). The protocol number of the study is PROSPERO CRD42018089295 (<https://www.crd.york.ac.uk/PROSPERO/>). We performed a literature search using PubMed, Scopus and EBSCO databases for relevant articles up to February 2018. The search strategy included the use of the following key words: (“depression” “major depression” “depressive disorders”), (“suicidal behavior” “suicide attempt” “completed suicide” “suicide ideation”), (“FKBP5” or “FK506 binding protein 51”) and (“rs1360780” or “rs3800373” or “rs4713916”). We limited the languages to English. The references from retrieved articles were also searched.

2.2. Eligibility criteria

To be eligible the studies had to meet the following criteria: (1) case-control studies evaluating an association between *FKBP5* rs1360780, rs3800373 and rs4713916 polymorphisms and depressive disorders or suicidal behavior risk; (2) both cases and controls had to be clearly diagnosed and all controls had to be healthy subjects, and (3) the studies included information that allow for calculation of odds ratios (ORs) and 95% confidence intervals (CIs).

2.3. Data extraction and quality assessment

Data were independently extracted from each study by two investigators and then inserted into a standardized table. The table included the following information: last name of first author, year of publication, country of origin, diagnoses, sample sizes of cases and controls, males included in cases and controls, genotyping methods used and genotype distribution. We applied the Newcastle Ottawa Scale (NOS) to evaluate the methodological quality of the eligible studies

[45]. Accumulated scores ranged from 0 to 9 points; scores of 0–5 and 6–9 were considered low and high quality respectively. Disagreements were resolved by discussion.

2.4. Statistical analysis

All analyses were conducted using the Comprehensive Meta-Analysis v2.2 software. The distribution of genotypes in the control groups, were tested by Hardy-Weinberg equilibrium (HWE) using the Chi-square test. Cochran's chi-square-based Q statistic test and the inconsistency index (I^2) were applied to examine the statistical heterogeneity among studies. When no obvious heterogeneity existed across the studies ($P > 0.05$ or $I^2 < 50\%$), we pooled the ORs using the random effects model (DerSimonian and Laird) (George and Aban, 2016). The following genetic models were evaluated: allele comparison (B vs. A), homozygote comparison (BB vs. AA), heterozygote comparison (AB vs. AA), recessive comparison (BB vs. AA + AB), and dominant comparison (BB + AB vs. AA). “A” represents the wild allele, while “B” represents the mutant allele. The ORs and its 95% CI were used to evaluate the pooled effect size. In addition, we conducted subgroup analyses by ethnicity (Caucasian) or diagnostic (major depression or completed suicide). However, the pooled analyses on subgroups were performed only when there were at least 2 studies in each subgroup for each polymorphism.

2.5. Publication bias and sensitivity analysis

The potential publication bias was evaluated by Begger's funnel plots. Funnel-plot asymmetry was further assessed using the Egger's linear regression test ($P > 0.05$) (Peters et al., 2006). To evaluate the stability of the results in this meta-analysis, we performed a sensitivity analysis by sequentially excluding each study and rechecked whether the pooled ORs were altered significantly.

3. Results

3.1. Characteristics of the studies included

We identified 173 potentially relevant publications. After screening and assessing the publications according to the inclusion/exclusion criteria, only twelve publications were included in the final analysis (Fig. 1). The studies selected were published between 2006 and 2017. Eight studies evaluated Caucasian populations, two evaluated Asian populations, one study was conducted in African-American people and the last study was conducted in White non-Hispanic or Black ethnicities. The distribution of genotypes in controls did not deviate from HWE. NOS scores in this systematic review ranged from 6 to 9. A summary of the risk of bias assessed through the NOS for case-control studies, is shown in Fig. 2 and Table 1. We included nine case-control studies for depressive disorders (Gawlik et al., 2006; Han et al., 2017; Lahti et al., 2016; Lavebratt et al., 2010; Lekman et al., 2008; Minelli et al., 2013; Papiol et al., 2007; Szczepankiewicz et al., 2014; Zobel et al., 2010). The cases were confirmed using DMS-IV, SCID-I, ICD-10 and BDI scales and 6 studies adopted Real-time PCR as the detection method. For suicidal behavior we included three cases-control studies (Supriyanto et al., 2011; Fudalej et al., 2015; Yeo et al., 2017); the which were confirmed using DMS-IV and ICD-10 scales; Real-time PCR as the detection method was used in the three studies. Tables 1 and 2 list the essential features of the studies included in this meta-analysis.

3.2. Meta-analysis of rs1360780 vs. depressive disorders or suicidal behavior

Nine studies reported the rs1360780 polymorphism in patients with depressive disorders and healthy controls, a total of 3955 cases and 5647 controls. The random effects meta-analysis showed no evidence of

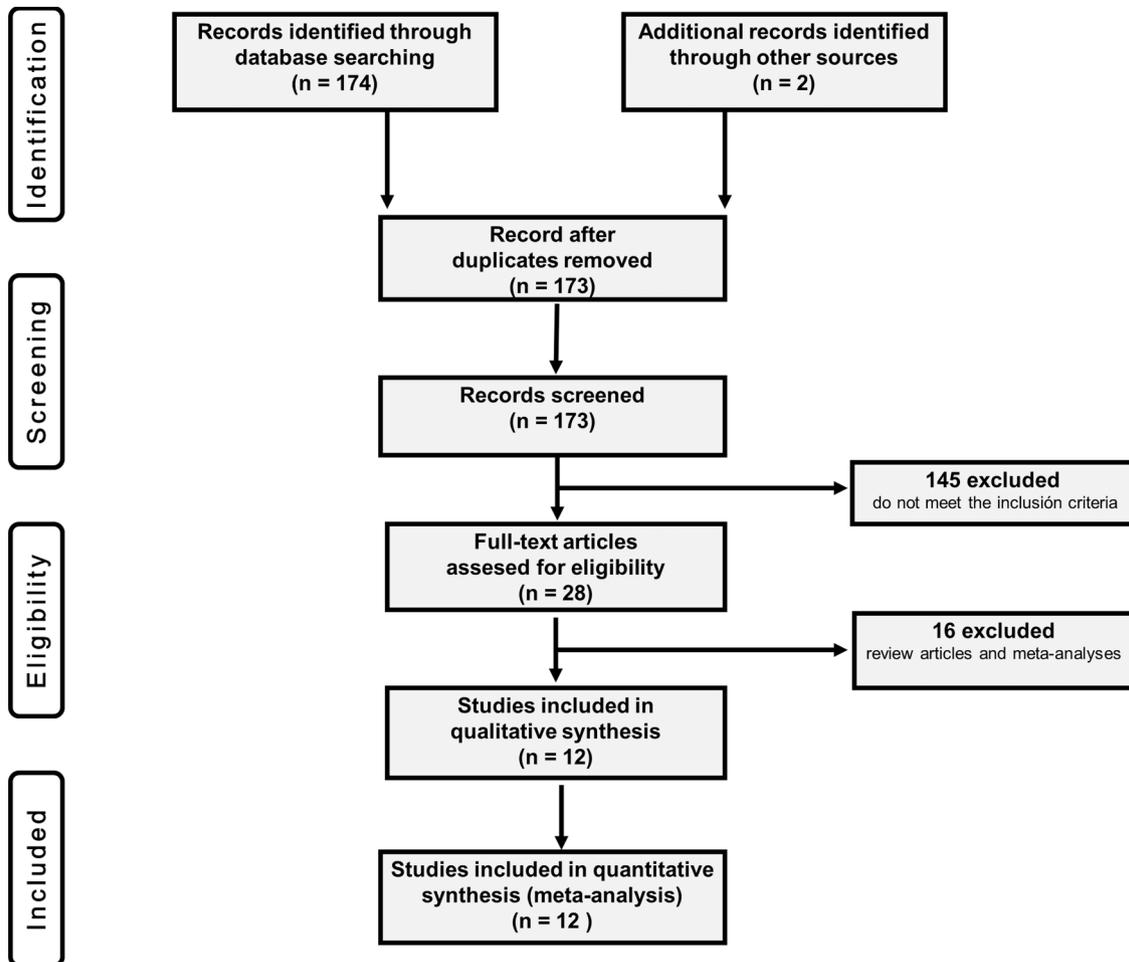


Fig. 1. Flow chart representing the studies identification and screening.

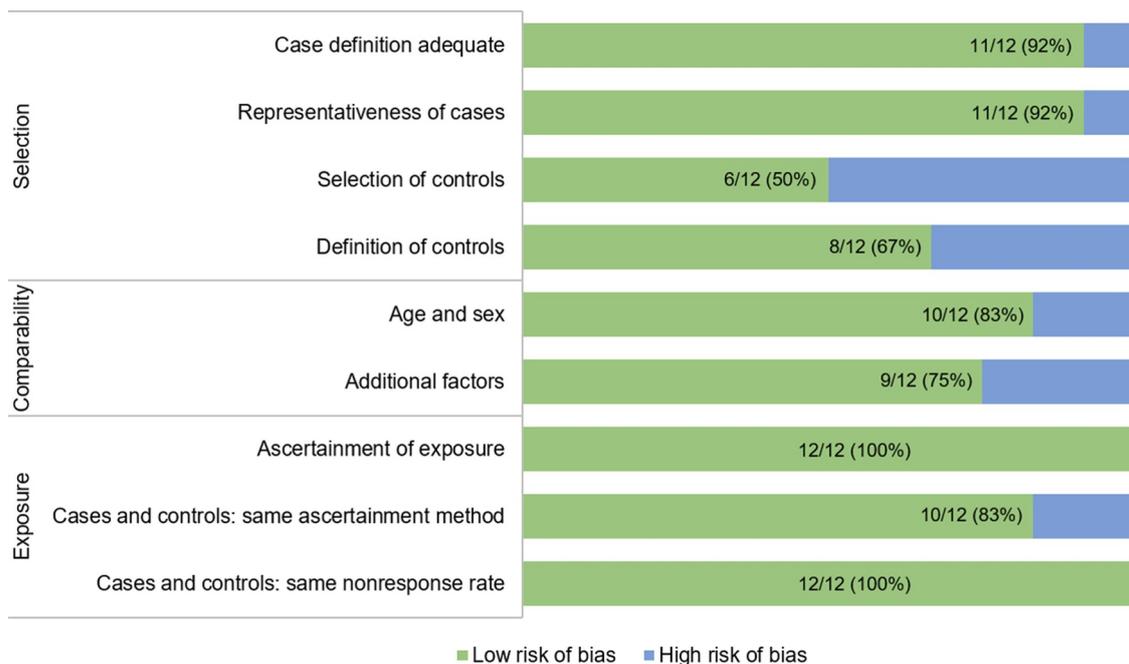


Fig. 2. Quality evaluation of the included studies based on the Newcastle Ottawa Scale.

Table 1
Characteristics of the 12 studies included in the meta-analysis.

Study rs1360780	Year	Country	Diganostic tool	Disease	Case/Control	Males Case/Control	Cases		Controls		HWE	NOS score		
							CC	CT	TT	CC			CT	TT
Gawlik, M. (Gawlik et al., 2006)	2006	Germany	ICD-10	Monopolar depression	248/188	154/105	114	110	24	94	74	20	0.34	8
Papiol, S. (Papiol et al., 2007)	2007	Spain	DSM-IV and SCID-I	Major depression	157/91	35/55	72	65	20	45	38	8	0.99	9
Lekman, M. (Lekman et al., 2008)	2008	Sweden	DSM-IV	Non-psychotic major depression	1520/739	–	638	712	170	360	290	89	0.11	7
Lavebratt, C. (Lavebratt et al., 2010)	2010	Sweden	DSM-IV	Major depression	431/2204	105/910	236	159	36	1200	841	163	0.35	7
Zobel, A. (Zobel et al., 2010)	2010	Germany	DSM-IV	Unipolar depression	267/284	98/115	136	112	19	122	131	31	0.63	8
Minelli, A. (Minelli et al., 2013)	2013	Italy	DSM-IV	Major depression	657/462	210/203	300	304	53	207	203	52	0.83	6
Szczepankiewicz, A. (Szczebankiewicz et al., 2014)	2014	Poland	DSM-IV and SCID-I	Major depression	218/513	50/315	106	102	10	282	198	33	0.82	7
Lahti, J. (Lahti et al., 2016)	2016	Finland	BDI	Depression	343/1078	75/443	210	124	9	667	361	50	0.89	8
Han, K-M. (Han et al., 2017)	2017	Republic of Korea	DSM-IV and SCID-I	Major depression	114/88	24/27	72	39	3	58	29	1	0.20	7
Supriyanto, I. (Supriyanto et al., 2011)	2011	Japan	DSM-IV	Completed suicide	215/228	144/149	127	69	19	139	79	10	0.77	7
Fudalej, S. (Fudalej et al., 2015)	2015	Poland	ICD-10	Completed suicide	520/462	428/259	278	207	35	279	161	22	0.84	7
Yeo, S. (Yeo et al., 2017)	2017	USA	DSM-IV	Suicide attempt	16/13	–	9	5	2	4	7	2	0.71	8
rs3800373							AA	AC	CC	AA	AC	CC		
Gawlik, M. (Gawlik et al., 2006)	2006	Germany	ICD-10	Monopolar depression	248/188	154/105	19	114	115	15	71	102	0.59	8
Lekman, M. (Lekman et al., 2008)	2008	Sweden	DSM-IV	Non-psychotic major depression	1256/634	–	673	666	157	349	272	70	0.11	7
Zobel, A. (Zobel et al., 2010)	2010	Germany	DSM-IV	Unipolar depression	268/284	98/115	14	108	146	26	130	127	0.37	8
Szczepankiewicz, A. (Szczebankiewicz et al., 2014)	2014	Poland	DSM-IV and SCID-I	Major depression	220/516	50/315	116	96	8	298	184	34	0.44	7
Supriyanto, I. (Supriyanto et al., 2011)	2011	Japan	DSM-IV	Completed suicide	219/228	144/149	128	75	11	141	75	10	0.99	7
Fudalej, S. (Fudalej et al., 2015)	2015	Poland	ICD-10	Completed suicide	493/475	428/259	250	180	38	274	249	23	0.64	7
Yeo, S. (Yeo et al., 2017)	2017	USA	DSM-IV	Suicide attempt	16/13	–	9	5	2	4	7	2	0.71	8
rs4713916							CC	CT	TT	CC	CT	TT		
Gawlik, M. (Gawlik et al., 2006)	2006	Germany	ICD-10	Monopolar depression	248/188	154/105	107	122	19	96	74	18	0.50	8
Lekman, M. (Lekman et al., 2008)	2008	Sweden	DSM-IV	Non-psychotic major depression	1256/634	–	801	606	116	414	264	331	0.26	7
Zobel, A. (Zobel et al., 2010)	2010	Germany	DSM-IV	Unipolar depression	268/284	98/115	136	118	14	127	121	37	0.33	8
Szczepankiewicz, A. (Szczebankiewicz et al., 2014)	2014	Poland	DSM-IV and SCID-I	Major depression	222/521	50/315	107	104	11	283	207	31	0.39	7

BDI: Beck Depression Inventory; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders; ICD-10: International Statistical Classification of Diseases and Related Health Problem; NOS: Newcastle–Ottawa Scale; SCID-I: Structured Clinical Interview for DSM.

Table 2
Main data of all studies included in the meta-analysis.

Author	Diagnosis	Population	Sample collected	Genotyping method	Outcomes reported	Limitations
Depressive disorder						
Gawlik, M. (Gawlik et al., 2006)	Monopolar and manic depression	Caucasian	Blood	Real-time PCR (TaqMan)	Not association	Unspecified
Papiol, S. (Papiol et al., 2007)	Major depression	Caucasian	blood	Real-time PCR (TaqMan)	Not association	Unspecified
Lekman, M. (Lekman et al., 2008)	Non-psychotic major depression	Non-Hispanic and black race	Blood	Real-time PCR (TaqMan)	Association of the marker rs1360780 with disease. This association was only seen in non-Hispanics	Unspecified
Lavebratt, C. (Lavebratt et al., 2010)	Major depression	Caucasian	Saliva	Real-time PCR (TaqMan)	Association of the rs1360780 polymorphism only in men	The study was based on a small sample population
Zobel, A. (Zobel et al., 2010)	Unipolar depression	Caucasian	Blood	Real-time PCR (TaqMan)	Association of rs4713916, rs3800373, rs1360780 polymorphisms with the disease status of unipolar depression	Unspecified
Minelli, A. (Minelli et al., 2013)	Major depression	Caucasian	Unspecified	Unspecified	T allele of rs1360780 was more frequent among the patients affected by major depression with a comorbidity of anxiety disorders	Homogeneity of the study sample
Szczepankiewicz, A. (Szczeppankiewicz et al., 2014)	Major depression	Caucasian	Blood	Real-time PCR (TaqMan)	Association between five <i>FKBP5</i> polymorphisms (rs1360780, rs9470080, rs4713916, rs9296158 and rs9394309) and major depressive disorder	- Low power statistical - The study was based on a small sample population
Lahti, J. (Lahti et al., 2016)	Depression	Caucasian	Blood.	Sequencing	Association of rs1360780, rs9470080, rs9394309 polymorphisms with depressive symptoms	Lack of data
Han, K-M. (Han et al., 2017)	Major depression	Asian	Blood	PCR	The T allele of rs1360780 was associated with significant volume reductions in brain regions, only in the MDD group	- MDD patients were taking antidepressants - Not investigate HPA-axis activity - Lack of data
Suicidal behaviour						
Supriyanto, I. (Supriyanto et al., 2011)	Completed suicide	Asian	Blood	Real-time PCR (TaqMan)	Not association with SNP's, but if between haplotypes	- Not was perform further psychiatric disease-subdivided analyses for genetic associations because of the lack of clinical background information
Fudalej, S. (Fudalej et al., 2015)	Completed suicide	Caucasian	Cases: Blood Controls: Saliva	Real-time PCR (TaqMan)	Association of the rs3800373 polymorphism and haplotypes	- The study was based on a small sample population Psychiatric diagnoses were not available for all suicide victims
Yeo, S. (Yeo et al., 2017)	Suicide attempt	African American	Unspecified	Real-time PCR (TaqMan)	The rs1360780 locus alter <i>FKBP5</i> expression	The study was based on a small sample population

MDD: Major depression.

Table 3
Stratified analyses of the *FKBP5* polymorphism on depressive disorder or suicidal behavior risks in meta-analysis.

Study groups	Number	Genetic model		Heterogeneity I ² test (%)	Q test (P value)	Publication bias Egger test (P value)	Homozygote BB vs. AA OR (95% CI)	Heterogeneity I ² test (%)	Q test (P value)	Publication bias Egger test (P value)	Heterozygote AB vs. AA OR (95% CI)	P value
		B vs. A OR (95% CI)	Allele									
Depressive disorder												
rs1360780												
Overall	9	1.01 (0.93–1.10)	0.72	27	0.20	0.41	0.91 (0.74–1.11)	18	0.28	0.34	1.10 (0.97–1.26)	0.13
Major depression	6	1.01 (0.91–1.12)	0.80	0	0.58	0.09	0.95 (0.71–1.27)	14	0.32	0.22	1.06 (0.92–1.21)	0.40
Caucasian	7	0.97 (0.89–1.07)	0.61	12	0.33	0.27	0.84 (0.66–1.07)	19	0.28	0.42	1.04 (0.92–1.18)	0.48
rs3800373												
Overall	4	0.93 (0.74–1.17)	0.58	34	0.07	0.09	1.11 (0.73–1.69)	50	0.11	0.40	1.29 (1.11–1.51)	0.03
Caucasian	3	0.85 (0.68–1.08)	0.20	45	0.11	0.41	1.06 (0.51–2.22)	26	0.05	0.13	1.35 (1.03–1.78)	0.02
rs4713916												
Overall	4	0.80 (0.47–1.35)	0.41	96	0	0.06	0.47 (0.18–1.20)	41	0.16	0.06	1.19 (1.00–1.41)	0.03
Caucasian	3	0.98 (0.72–1.32)	0.90	24	0.12	0.41	0.67 (0.35–1.28)	61	0.07	0.11	1.20 (0.90–1.60)	0.20
Suicidal behavior												
rs1360780												
Overall	3	1.20 (0.98–1.48)	0.06	16	0.30	0.09	1.65 (1.05–2.58)	0	0.45	0.24	1.06 (0.72–1.56)	0.75
Completed suicide	2	1.24(1.05–1.48)	0.07	0	0.73	–	1.74(1.10–2.75)	0	0.59	–	1.15(0.87–1.53)	0.31
rs3800373												
Overall	3	1.17 (0.89–1.55)	0.24	41	0.18	0.07	1.54 (0.97–2.43)	0	0.41	0.07	1.16 (0.82–1.63)	0.38
Completed suicide	2	1.26(1.05–1.51)	0.09	0	0.30	–	1.62(1.01–2.58)	0	0.45	–	1.24(0.99–1.56)	0.05
Depressive disorder												
rs1360780												
Overall	40	0.09	0.26	0.87 (0.73–1.03)	0.11	0.39	1.07 (0.94–1.21)	5	0.27	0.49	1.00 (0.87–1.14)	0.31
Major depression	0	0.52	0.26	0.93 (0.67–1.29)	0.68	0.22	1.04 (0.91–1.19)	29	0.51	0.28	1.00 (0.87–1.14)	0.14
Caucasian	13	0.32	0.34	0.83 (0.65–1.05)	0.13	0.27	1.01 (0.90–1.14)	20	0.82	0.36	1.00 (0.87–1.14)	0.31
rs3800373												
Overall	0	0.95	0.16	0.95 (0.65–1.37)	0.78	0.09	1.25 (1.08–1.45)	40	0.05	0.19	1.00 (0.87–1.14)	0.35
Caucasian	0	0.91	0.39	0.95 (0.65–1.37)	0.78	0.07	1.22 (1.09–1.55)	30	0.04	0.19	1.00 (0.87–1.14)	0.32
rs4713916												
Overall	24	0.26	0.45	0.43 (0.17–1.06)	0.06	0.10	1.73 (1.22–2.46)	41	0.08	0.08	1.00 (0.87–1.14)	0.07
Caucasian	49	0.13	0.42	0.61 (0.37–1.01)	0.05	0.18	1.98 (1.50–2.63)	40	0.09	0.14	1.00 (0.87–1.14)	0.49
Suicidal behavior												
rs1360780												
Overall	49	0.14	0.10	1.58 (1.01–2.45)	0.04	0.59	1.15 (0.82–1.60)	0	0.4	0.38	1.00 (0.87–1.14)	0.05
Completed suicide	32	0.22	–	1.63(1.04–2.56)	0.03	0.43	1.26(1.00–1.53)	0	0.06	–	1.00 (0.87–1.14)	–
rs3800373												
Overall	37	0.2	0.06	1.44 (0.92–2.25)	0.10	0.69	1.18 (0.82–1.69)	0	0.35	0.11	1.00 (0.87–1.14)	0.06
Completed suicide	0	0.45	–	1.48(0.94–2.34)	0.08	0.53	1.29(1.04–1.60)	0	0.05	–	1.00 (0.87–1.14)	–

Statistical associations are shown in bold.

a significant association between this SNP and depressive disorders. In all the genetic models evaluated, the analyses of the overall population as well as by subgroups revealed no statistical associations between rs1360780 and depressive disorders; the results are shown in Table 3. However, when we evaluated the *FKBP5* C > T (rs1360780) polymorphism and suicidal behavior susceptibility using three studies (751 cases and 703 controls), there was an overall statistical association with the TT genotype; furthermore, the recessive model also showed a significant association (for BB vs. AA: OR = 1.65, 95% CI = 1.05–2.58, $Q = 0.45$, $I^2 = 0\%$; for BB vs. AA + AB: OR = 1.58, 95% CI = 1.01–2.45, $Q = 0.59$, $I^2 = 0\%$) (Fig. 3). When we stratified into a completed suicide subgroup (735 cases and 690 controls), we also found significant results (for B vs. A: OR = 1.24, 95% CI = 1.05–1.48, $Q = 0.73$, $I^2 = 0\%$; for BB vs. AA: OR = 1.74, 95% CI = 1.10–2.75, $Q = 0.59$, $I^2 = 0\%$; for BB vs. AA + AB: OR = 1.63, 95% CI = 1.04–2.56, $Q = 0.43$, $I^2 = 0\%$; for BB + AB vs. AA: OR = 1.26, 95% CI = 1.00–1.53, $Q = 0.38$, $I^2 = 0\%$) (Table 3).

3.3. Meta-analysis of rs3800373 vs. depressive disorders or suicidal behavior

In this meta-analysis we evaluated 1992 depressive disorders cases vs. 1622 controls (from four studies), the results revealed statistical associations when using the heterozygote model and dominant model (for AB vs. AA: OR = 1.29, 95% CI = 1.11–1.51, $Q = 0.95$, $I^2 = 0\%$; for BB + AB vs. AA: OR = 1.25, 95% CI = 1.08–1.45, $Q = 0.68$, $I^2 = 0\%$) (Fig. 4). To eliminate the effects of ethnic heterogeneity, we conducted a subgroup analysis evaluating only Caucasian populations (736 cases and 988 controls). We observed that this polymorphism was associated with depressive disorders in Caucasian individuals (for AB vs. AA: OR = 1.35, 95% CI = 1.03–1.78, $Q = 0.91$, $I^2 = 0\%$; for BB + AB vs. AA: OR = 1.22, 95% CI = 1.09–1.55, $Q = 0.56$, $I^2 = 0\%$) (Fig. 4). With regards of suicidal behavior, three studies comprising 728 cases with suicidal behavior and 716 healthy controls met the inclusion criteria; however, our analysis did not show a significant association between rs3800373 polymorphism and suicidal behavior (Table 3). In the stratified analysis for completed suicide (712 cases and 703 controls), the meta-analysis showed that the C-allele of rs3800373 was associated with the disease (for B vs. A: OR = 1.26, 95% CI = 1.05–1.51, $Q = 0.30$, $I^2 = 0\%$; for BB vs. AA: OR = 1.62, 95% CI = 1.01–2.58, $Q = 0.45$, $I^2 = 0\%$; for BB vs. AA + AB: OR = 1.29, 95% CI = 1.04–1.60, $Q = 0.35$, $I^2 = 0\%$) (Table 3).

3.4. Meta-analysis of rs4713916 vs. depressive disorders

Four studies comprising 1994 cases and 1627 controls were eligible. The pooled ORs indicated that rs4713916 polymorphism was significantly associated with an increased risk of depressive disorders in two genetic models (for AB vs. AA: OR = 1.19, 95% CI = 1.00–1.41, $Q = 0.26$, $I^2 = 24\%$; for BB + AB vs. AA: OR = 1.73, 95% CI = 1.22–2.46, $Q = 0.14$, $I^2 = 45\%$) (Fig. 5). For Caucasian populations, three association studies comprising 738 cases and 993 controls met our criteria. As shown in Fig. 5, only the analysis using the dominant model showed an association between the polymorphism and a significant risk of depressive disorders (BB + AB vs. AA: OR = 1.98, 95% CI = 1.50–2.63, $Q = 0.10$, $I^2 = 36\%$).

3.5. Sensitivity analysis

We used the method of eliminating studies one by one to conduct the sensitivity analysis. The results proved stability in our study, since no significant changes were detected after removing each individual study and rechecking the pooled ORs and 95% CIs, which supported the reliability and robustness of our analysis.

3.6. Publication bias

We used Egger's test and funnel plot to examine the effect of publication bias. As can be observed in Figs. 3–5 and Table 3, no obvious publication bias was found. In addition, the results showed that P values of Egger's test in all models were >0.05 and the funnel plots were symmetrical, which indicated that there was no publication bias. Nevertheless, the publication bias could not be estimated for the completed suicide subgroup analyses due to the small sample size.

4. Discussion

FKBP51 is a chaperone protein that has been intensely investigated in several biology fields, receiving attention in current research on stress-related phenotypes and diseases such as posttraumatic stress disorder, major depression and suicide (Criado-Marrero et al., 2018; Fries et al., 2017). In our meta-analysis, we did not find any significant association between rs1360780 polymorphism and risk of depressive disorders in the overall analysis; this no association was also observed in the Caucasian subgroup, or the major depression subgroup. On the other hand, we found two previous meta-analyses that focused on overall major depression risk and *FKBP5* gene polymorphisms (Rao et al., 2016; Wang et al., 2018). Both studies reported a positive association between rs1360780 T-allele and major depressive disorder. However, in our study we did not find any evidence of association between *FKBP5* rs1360780 polymorphism and major depression; this contrast may be due to the difference in sample size, ethnicity, age, sex, and gene-environment, which increases the complexity of the genotype-phenotype association. Nevertheless, psychiatric diseases are the result of a complex interplay of genes and environmental factors; therefore, several studies have focused on gene-environment interactions (GxEs) occurring at genetic loci involved in the stress response, for example the locus of *FKBP5* (Scheuer et al., 2016; Zannas and Binder, 2014). Then, the rs1360780 polymorphism could be exposing a weak or nearly no effect on depressive disorders susceptibility; the influence of this genetic variant may be masked by other yet unidentified causal genes involved in the disease.

For the rs3800373 polymorphism we found that individuals with the minor C allele, had an increased risk of developing depressive disorder in the overall population. In addition, a strong association was also identified in the Caucasian population; nevertheless, the previous meta-analyses did not evaluate ethnicity in their analyses and we could not compare our findings. This SNP has been reported to be associated with increased *FKBP51* protein expression in peripheral blood, affecting the translation process and protein stability (Binder et al., 2008; Tatrot et al., 2009).

We also observed that the rs4713916 polymorphism was related to an increased risk of depressive disorders in the overall population and in the Caucasian subgroup. (Zobel et al., 2010) previously found a significant association between *FKBP5* variants (rs3800373 and rs4713916) and depression; they reported a decreased hippocampal volume and response to antidepressants in association with *FKBP5* risk alleles. Their study comprised 268 German in-patients with recurrent unipolar depression and 284 German controls. Zobel et al. reported that this SNP was associated with vulnerability to unipolar depression, hypothalamic-pituitary-adrenal axis activity after citalopram treatment, as well as with right hippocampal volume.

As for suicidal behavior, this is the first meta-analysis that investigates the association between *FKBP5* polymorphisms and this disease. Our results were positive for the rs1360780 polymorphism in the overall population as well as for the completed suicide subgroup. In addition, a strong association was identified between rs3800373 and the completed suicide subgroup. Previous studies have shown that after childhood trauma, rs1360780 and rs3800373 interact, increasing the risk of stress related disorders and suicide (Binder et al., 2008; Roy et al., 2010). The rs1360780 and rs3800373 locus alters *FKBP5*

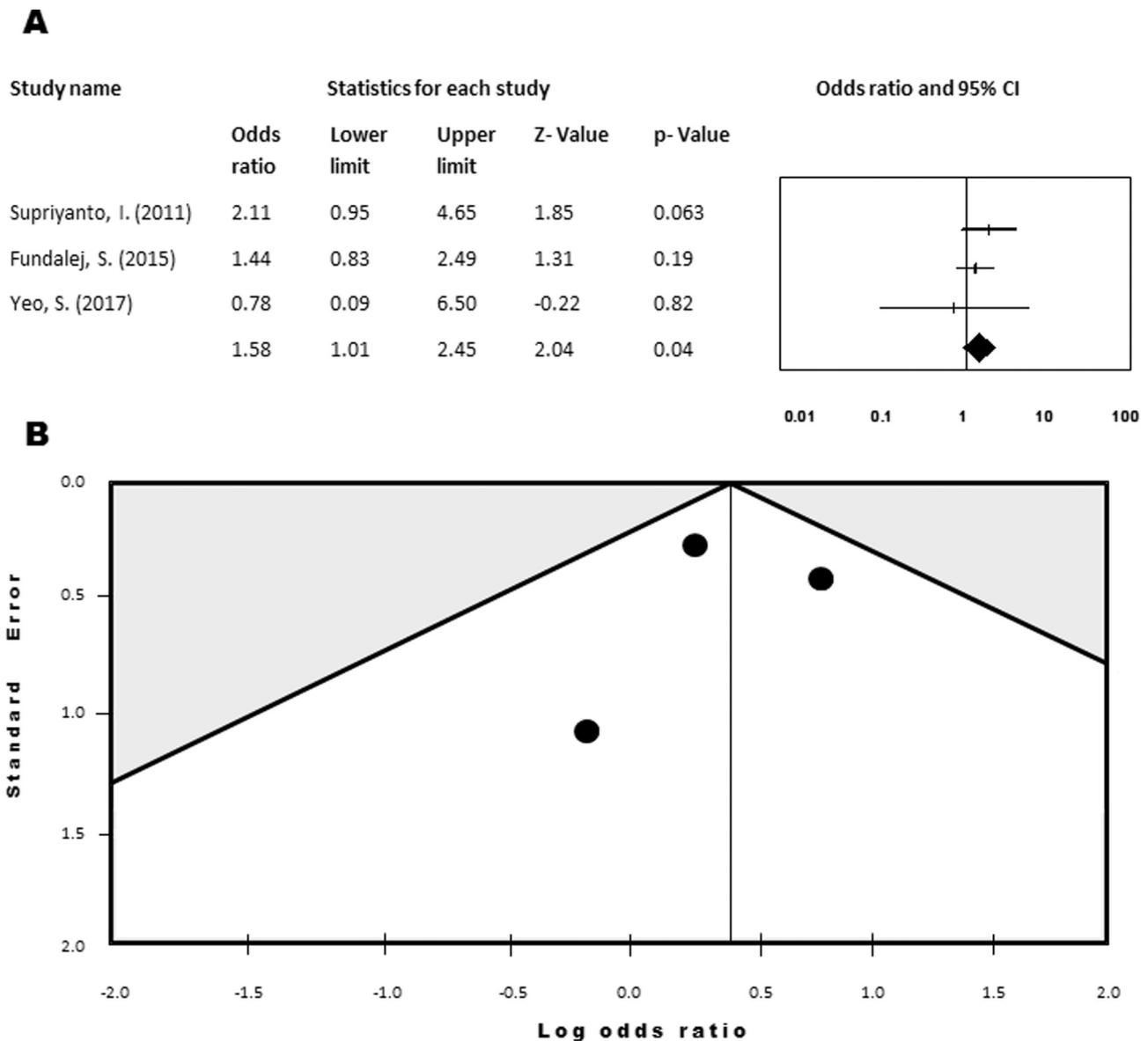


Fig. 3. Meta-analysis for the association between the risk of suicidal behavior and rs1360780 polymorphism. A) Forest plot (BB vs. AA + AB). B) Begg's funnel plot for publication bias tests (BB vs. AA + AB).

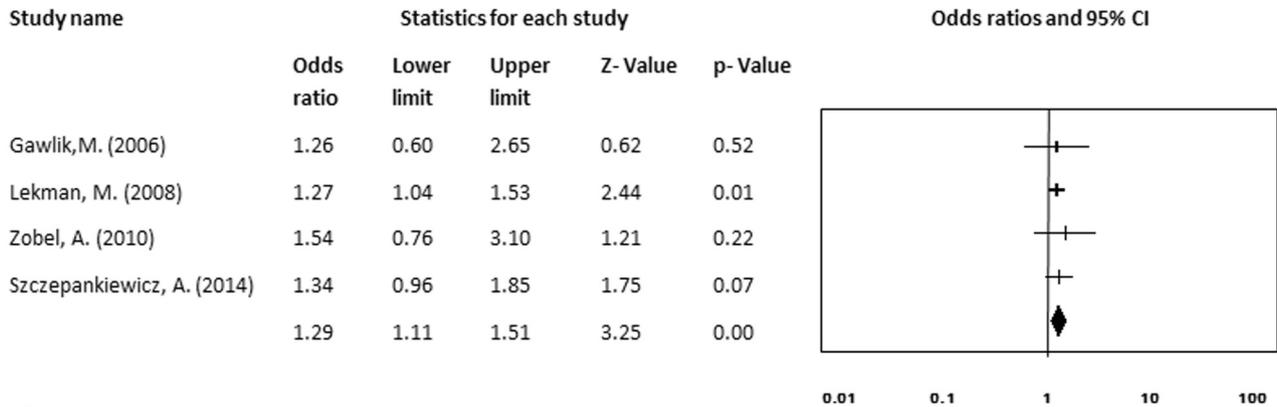
expression, further that in trans-fashion, this locus affects the expression of other glucocorticoid-regulated genes; a prolonged or excessive activation of the glucocorticoid receptor reduces the glucocorticoid receptor sensitivity, and an impaired negative feedback of the hypothalamic-pituitary-adrenal axis has been implicated in the pathogenesis of suicide (Yeo et al., 2017). The results of the present study along with previous reports indicate that genetic alterations in *FKBP5* gene may influence vulnerability to suicide; nevertheless, due to our small sample size, future studies that include larger sample sizes are needed. More than

The current findings need to be interpreted with caution, as psychiatric diseases are the result of a complex interplay of genes and environmental factors (Scheuer et al., 2016; Zannas and Binder, 2014). Interactions between *FKBP5* gene variants and early-life adversity or stress may enhance the risk of a range of psychiatric disorders in adulthood (Wang et al., 2018). Several studies have found that early-life adversities impact the subsequent risk of disease via affecting the hypothalamic-pituitary-adrenal axis (Jurueña, 2014; van Bodegom et al., 2017; Wang et al., 2018). This is likely to occur when an early-life diversity is combined with genetic predispositions that together have

critical effects on the brain and behavior. This has been observed in 31 independent studies comprising 39 cohorts with more than 31,000 ethnically and clinically diverse patients, that have investigated interactions of *FKBP5* with early life adversity and depression, anxiety, posttraumatic stress disorder, suicide attempts, aggression, alcohol and substance use disorders, psychosis and psychiatric symptoms (Matosin et al., 2018).

Literature indicates that polymorphisms that showed a positive association in this meta-analysis, have a role in early life stress. Wang et al. (2018) found a highly significant association between rs3800373 and an increased risk of developing depression after childhood adversity in 7135 individuals. The T-risk allele (rs4713916) also interacts with lifetime trauma predicting a higher risk of major depression disorder (Zimmermann et al., 2011). After childhood trauma (but not after adulthood trauma), it predicts greater posttraumatic stress disorder symptomatology (Binder et al., 2008); furthermore, after childhood trauma it predisposes psychotic symptoms (Collip et al., 2013). A different study evaluated the influence of rs1360780 over the expression of *FKBP5* dependent on childhood trauma exposure in patients with suicidal behavior diagnoses. This study clearly showed cis

A



B

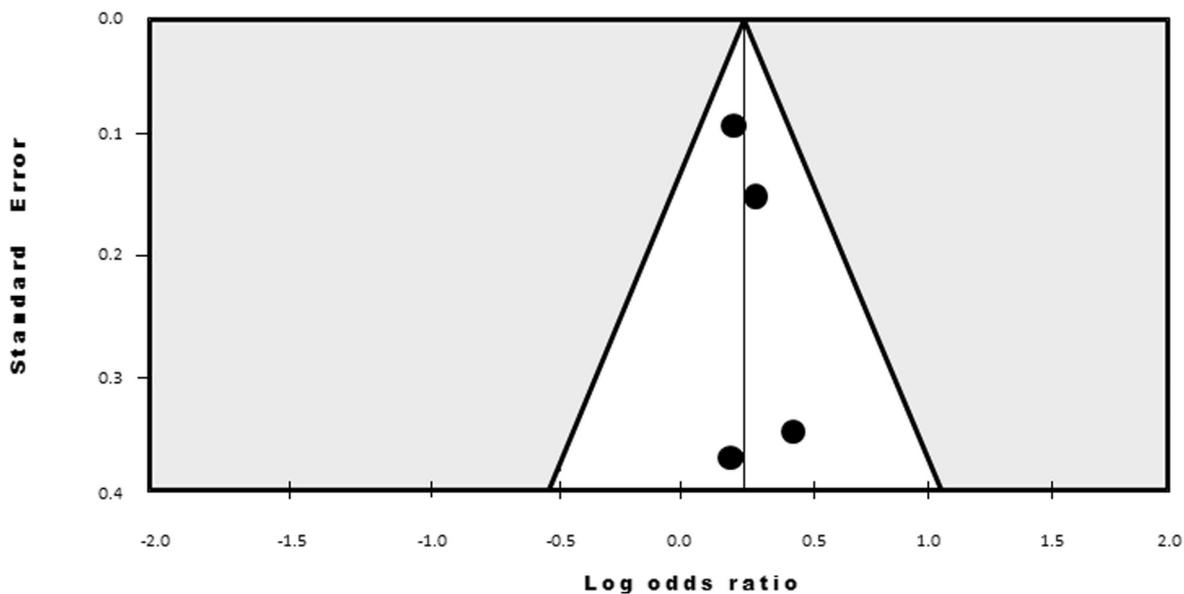


Fig. 4. Meta-analysis for the association between the risk of depressive disorder and rs3800373 polymorphism in the overall population. A) Forest plot (AB vs. AA). B) Begg's funnel plot for publication bias tests (AB vs. AA).

and trans effects of rs1360780 on gene regulation and combined effects with exposure to childhood trauma (Yeo et al., 2017).

More than 30 genetic studies suggest that common adverse life events are associated with *FKBP5* for several psychiatric disorders in more than 31,000 patients, which suggests genetic mechanisms. Matosin et al. (2018) propose that epigenetic effects are exacerbated in carriers of *FKBP5* variants, such as rs1360780 that is associated with an enhanced glucocorticoid receptor-induced mRNA induction. When altering *FKBP5* responsivity, the alleles can change glucocorticoid receptor sensitivity and produce a negative feedback of the hypothalamic-pituitary-adrenal axis, disinhibiting *FKBP5* transcription and affecting the cortisol secretion with molecular, cellular, and endocrine consequences. On the other hand, the absence of interaction or association of adult trauma with *FKBP5* genotypes suggests an additional molecular mechanism for *FKBP5* (Binder et al., 2008; Lahti et al., 2016). Based on literature, we suggest that *FKBP5* alleles change a person's susceptibility in combination to both negative (risk-favoring) and positive (development-enhancing) environmental events, following differential susceptibility theory (Ellis et al., 2011).

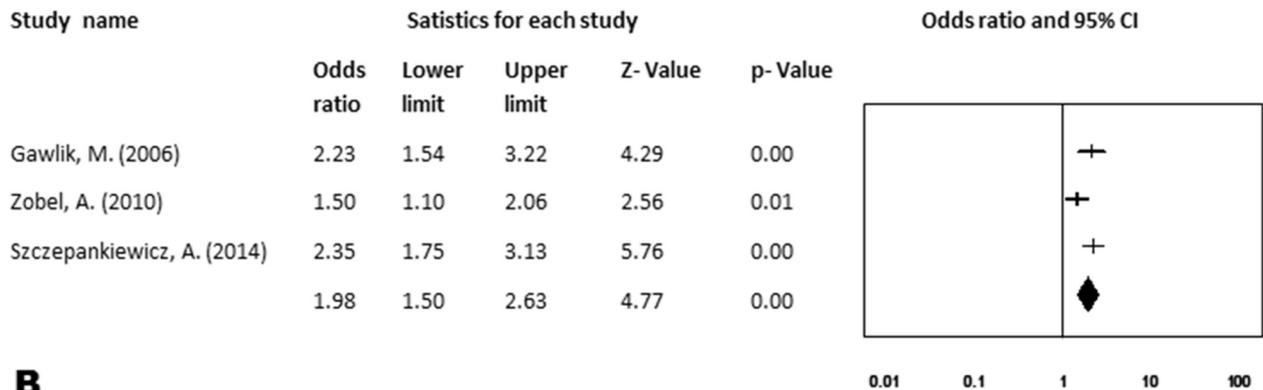
Overall, our results showed that the rs3800373 polymorphism is significantly associated with an increased risk of depressive disorders and completed suicide. This finding suggests a shared genetic etiology

between these disorders; nevertheless, the rs1360780 polymorphism is involved in the development of suicidal behavior but not in depressive disorders. The mechanism by which the rs1360780 polymorphism influences susceptibility to suicidal behavior is poorly understood. Our observations could indicate different susceptibility to develop suicidal behavior or depressive disorder, and this characteristic may have potential disease-specific therapeutic implications.

We consider that our study is stronger than previous meta-analyses, because our pooled analysis systematically excluded studies lacking of data and the quality of all of the trials was high, with NOS above 6 points. Furthermore, we analyzed five genetic models to explore inheritance patterns of genes.

However, our study has some limitations and some sub-analyses could not be carried out. First, the numbers of studies as well as simple sizes for subgroups were limited. Second, several risk factors, such as age, gender, environment–gene interaction and different characteristics of life style, may affect the susceptibility to psychiatric disorders. Depressive disorders and suicidal behavior are complex diseases involved in the regulation of a series of genetic factors besides *FKBP5*. As multifactorial diseases, the risk of developing them is closely related to various elements, and not just a single factor. However, no further analyses could be conducted in our evaluation due to lack of studies

A



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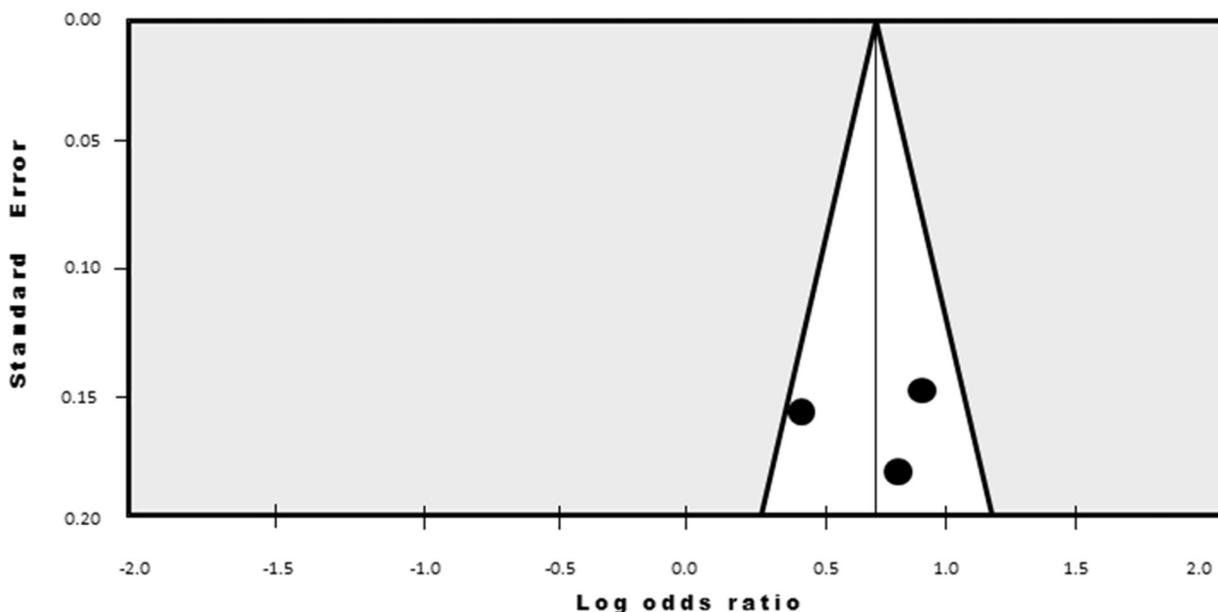


Fig. 5. Meta-analysis for the association between the risk of depressive disorder and rs4713916 polymorphism in Caucasian population. A) Forest plot (BB + AB vs. AA). B) Begg's funnel plot for publication bias tests (BB + AB vs. AA).

that met the inclusion criteria. Therefore, more raw data are needed to adjust other variables, such as age, gender, and life style. Type and timing of some adversities during childhood influence the development of SB/Depression; however, we did not take this possibility into consideration. Third, language bias, as we only selected articles written in English, we could not include more studies. Fourth, our meta-analysis included studies that performed different comparisons (i.e. suicide attempt vs. completed suicide; various subcategories of depression); hence, caution must be taken when generalizing these results to the suicide behavior or depressive disorders. Nevertheless, this meta-analysis provides an estimation of the role of FKBP5 in suicide behavior or depressive disorders. Another fact to take into consideration is the methodological limitations of the studies included in the analysis of suicide (see Table 2). Concerning this, the limitations stipulated in these researches could easily bias the results that could lead to misinterpretations of the present findings; hence, it is necessary to perform further studies in order to increase the power to detect the small effect that could have FKBP5 variant and thus to be able to have decisively outcomes.

Finally, we did not verify the possible association of FKBP5 polymorphisms in relation to different ethnicities; therefore, the conclusions may not be applicable to other populations. Despite these limitations, a

strict protocol, data identification, and statistical analysis were performed to reduce potential bias in our analysis.

5. Conclusion

In conclusion, we found that the role of the FKBP5 polymorphisms differs by the type of disease. Our meta-analysis results indicate that C (rs3800373) and T (rs4713916) risk alleles are statistically associated with a risk of presenting depressive disorders. We also observed that FKBP5 rs1360780 and rs3800373 polymorphisms are involved in the development of suicidal behavior and completed suicide, respectively. Nevertheless, interactions of gene variants and environmental risk factors should be considered in future studies; larger samples and different ethnic groups should be studied in order to have a better understanding of the association between the FKBP5 polymorphisms and depressive disorders or suicidal behavior risks.

Conflict of interest statement

The authors have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.066.

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