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META-ANALYSIS

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# Association of *OXTR* polymorphism (*rs53576*) with depression: a meta-analysis

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## Abstract

**Background** Depression is a common psychiatric disorder that negatively affects mood and thoughts. Association studies of *OXTR* polymorphisms with depression have been performed repeatedly. However, the results of these studies were inconsistent. The aim of the present study was to perform a meta-analysis of case–control studies that have investigated the relationship between the *OXTR* polymorphism (rs53576) and depression risk.

**Methods** Four databases, PubMed, ScienceDirect, Springer Link, and Google Scholar, were searched, and a total of 10 studies were involved in the meta-analysis. ReviewManager (RevMan) 5.4 software was used to perform a meta-analysis of the eligible studies.

**Results** A significant association between *OXTR* rs53576 and depression was found in the recessive model (Odds Ratio (OR) AA vs. AG + GG = 1.28, 95% Confidence Interval (CI) [1.02–1.59], $P = 0.03$), while there was no association with the other two genetic models (dominant model: OR AA + AG vs. GG = 1.01, 95% CI [0.87–1.18], $P = 0.87$; allelic model: OR A vs. G = 0.95, 95% CI [0.83–1.09], $P = 0.46$). A significant association was observed in the Caucasian populations (OR 1.29, 95% CI [1.01, 1.64], $P = 0.04$), while the Asian populations showed no significant association (OR 1.22, 95% CI [0.71, 2.09], $P = 0.48$).

**Conclusions** This meta-analysis is to date the first to provide a comprehensive investigation of the association of the *OXTR* rs53576 polymorphism with depression, and its results reflect the data currently available from the literature and can serve as a guide for further research.

**Keywords** *OXTR*, Depression, Polymorphism, Association, Meta-analysis

## Background

Depression is a common mental disorder and a leading cause of disability. According to World Health Organization (WHO), about 1 billion people have mental disorders and over 300 million people suffer from depression worldwide [3]. In the first year of the COVID-19 epidemic, the prevalence of anxiety increased by 25%. Depressive psychopathology was identified in around 35% of patients following infection with the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [27]. Scientists suggested that the significant increase could be a result of many factors, including fear of infection, financial worries, and social isolation during the pandemic.

Depression is assumed to be caused by the interplay of hereditary and external factors [15, 35]. Genetic factors have been frequently reported to play a significant role in the development of depression [1, 26].

Several genes' potential roles in the development of depression have been assessed in recent years. The most studied genes were oxytocin *OXT* and oxytocin receptor gene *OXTR*.

Oxytocin is a neuropeptide produced by the hypothalamus and well-known as a key regulator of human behavior and psychology. The role of oxytocin in social

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integration, aggression, and antisocial behavior, has been the subject of several studies in recent years [6]. Oxytocin exerts its effects via the oxytocin receptor (OXTR) [21].

OXTR is a G-protein-coupled receptor (GPCR), mostly expressed in the brain but also present in other body tissues, and has been proven to be involved in the development of social skills [38]. This prompted researchers to examine the OXTR gene as a prospective candidate for depression susceptibility.

The *OXTR* single nucleotide polymorphisms (SNPs) have been associated with human mental health issues [5]. The most studied SNP of *OXTR* so far is (rs53576) (G/A) in the third intron [19]. This polymorphism has been considered to be associated with human social and emotional behavior due to its potential modulatory effect on oxytocin-dopamine interactions [8]. Studying the influence of *OXTR* rs53576 on general behavior has been the subject of several studies to evaluate its role as a possible genetic marker for psychiatric disorders [24].

The aim of this study was to perform a meta-analysis of case–control studies that have investigated the association between the *OXTR* polymorphism (rs53576) and depression risk. Furthermore, subgroup analysis based on ethnicity was conducted to evaluate the association of this polymorphism with depression in Caucasian and Asian populations.

## Methods

### Study strategies

Meta-analysis was carried out according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [28]. Four databases (PubMed, ScienceDirect, Springer Link, and Google Scholar) were searched for case–control studies published in English up to January 2021 that investigated the association of OXTR rs53576 with depression risk in humans. The following keywords were used in the systematic search ("OXTR or oxytocin receptor", "Polymorphism or genetic variations", "rs53576", and "depression").

### Inclusion and exclusion criteria

Included studies had to meet the following criteria: 1) Published case–control studies involving human subjects; 2) Availability of data to calculate Odds Ratio (OR) with confidence interval (CI); and 3) Study the association between OXTR (rs53576) polymorphism and depression.

Exclusion criteria: 1) Reviews, meta-analyses, animal studies, duplication; 2) Irrelevant studies (investigated other diseases or other polymorphisms); and 3) Studies without sufficient information (genotype frequencies, controls).

### Data extraction

For each included study, the following data were extracted: 1) First author's surname 2) Year of publication 3) Country of origin 4) Sample size (case / control) 5) Genotyping data for cases and controls.

### Assessment of quality of included studies

The quality of the included studies was evaluated using the Newcastle–Ottawa Quality Assessment Form for Case–Control Studies. The results of the quality evaluation were considerable, with a minimum score of 8, which indicates the high quality of included studies.

### Statistical analysis

RevMan 5.4 (Cochrane Collaboration, London, UK) software was used to perform a meta-analysis of the eligible studies. The association between the *OXTR* (rs53576) polymorphism and depression risk was evaluated by OR with 95% CI in accordance with dominant and recessive inheritance models. Significant difference was considered when $P < 0.05$. Heterogeneity between studies was evaluated by a $chi^2$-based Cochran Q test and quantified with the $I^2$ statistic ($P < 0.05$ or $I^2 > 50\%$ indicated significant heterogeneity). For lower heterogeneity values, Fixed-effect model was used to calculate ORs and 95% CIs. Subgroup analysis was conducted on ethnicity of Caucasian and Asian populations. A sensitivity analysis was performed by sequentially excluding one study at a time. Publication bias was investigated using Begg's funnel plots.

## Results

### Characteristics of included studies

The flow chart of studies' selection and the reasons for exclusion are presented in Fig. 1. 162 articles were identified through database searching based on the keywords, 136 of these were excluded for the following reasons: 27 irrelevant articles, 38 duplicates, 24 reviews, 16 meta-analyses, 28 cohort studies, and 3 animal studies. The 26 remaining articles were assessed for eligibility. Of these, 16 articles were excluded for lack of sufficient information. A total of 10 eligible articles were included in the meta-analysis. An article studied two types of depression, and both types were considered separately.

The included studies were carried out in the Netherlands [33, 34], Republic of Korea [29], Poland [40], USA [4], Italy [11, 12], Australia [36], Canada [7], and Malaysia [23].

In all 10 included studies, total cases were 1847 and controls were 3673. The main characteristics of the included studies are shown in Table 1.

### Meta-analysis

The main results of meta-analysis and the heterogeneity test are presented in Table 2.

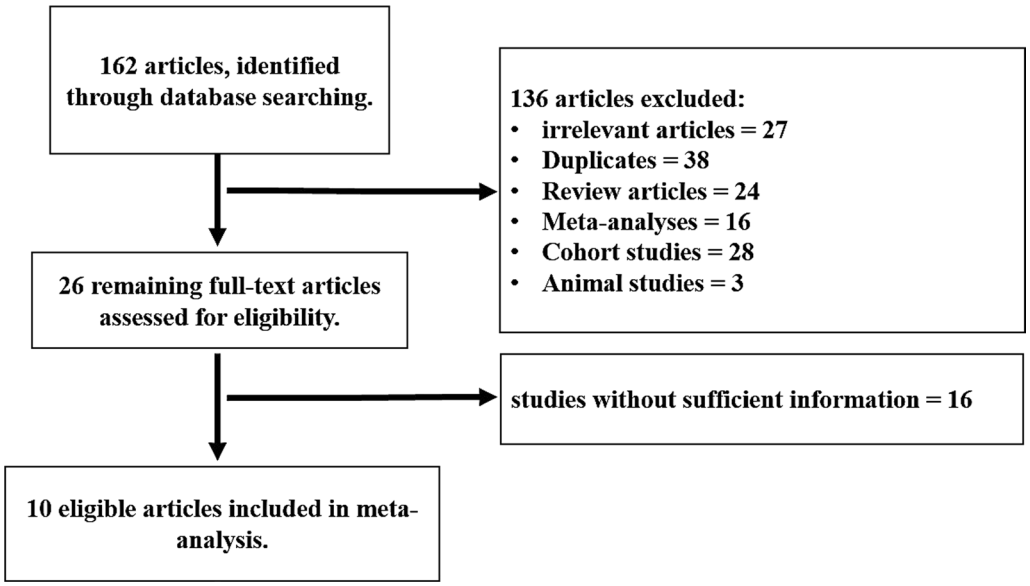


**Fig. 1** PRISMA Flow chart of study selection

**Table 1** Main characteristics of included studies in meta-analysis

| First author | Year | Country | Diagnosis | Cases (N) | Control (N) | HWE *P*-value* |
|---|---|---|---|---|---|---|
| Smarius | 2019 | Netherlands | Aggression/depression | 102 | 864 | 0.52 |
| Na | 2018 | Republic of Korea | Major depressive disorder (MDD) | 47 | 30 | 0.993 |
| Smarius | 2020 | Netherlands | Aggression/depression | 103 | 866 | 0.52 |
| Wasilewska | 2016 | Poland | Depression | 823 | 362 | > 0.5 |
| Bell | 2015 | USA | Postpartum depression (PPD) | 269 | 276 | 0.54 |
| Costa | 2017 | Italy | Depression | 188 | 225 | 0.222 |
| Thompson | 2014 | Australia | Maternal depression | 65 | 376 | 0.784 |
| Costa | 2009 | Italy | Unipolar depression | 93 | 192 | 0.2 |
| Costa | 2009 | Italy | Bipolar depression | 92 | 192 | 0.2 |
| Chagnon | 2015 | Canada | Anxiety/depression | 19 | 24 | - |
| Lee | 2019 | Malaysia | Depression | 46 | 266 | 0.68 |

* *HWE* Hardy–Weinberg equilibrium (all *p* values are > 0.05 and thus all controls are in accordance with HWE)

**Table 2** The association between OXTR polymorphism (rs53576) and depression risk

| Genetic models | Number of studies | Test of association | | | Test of heterogeneity | |
|---|---|---|---|---|---|---|
| | | OR | 95% CI | *P*-value | *P*-value | $I^2$ (%) |
| Dominant (AA + AG vs. GG) | 10 | 1.01 | [0.87–1.18] | 0.87 | 0.06 | 44 |
| Recessive (AA vs. AG + GG) | 9 | 1.28 | [1.02–1.59] | 0.03 | 0.96 | 0 |
| Allelic (A vs. G) | 8 | 0.95 | [0.83–1.09] | 0.46 | 0.13 | 37 |

According to the meta-analysis results, *OXTR* polymorphism (rs53576*)* has no significant association with depression in both allelic (Table 2, Fig. 2a) and dominant (Table 2, Fig. 2b) models.

The recessive model, on the other hand, shows significant association with the depression risk (Table 2, Fig. 2c) in both fixed effect (OR 1.28, 95% CI [1.02–1.59], $P=0.03$) and random effect (OR 1.29, 95% CI [1.04–1.60], $P=0.02$) models.

There is no significant heterogeneity in the studied models (Dominant: $I^2=44\%$, $p=0.06$, Recessive: $I^2=0\%$, $p=0.96$, Allelic: $I^2=37\%$, $p=0.13$) (Table 2).

Begg's funnel plot was used to estimate the publication bias of the included articles. The funnel plots of all the

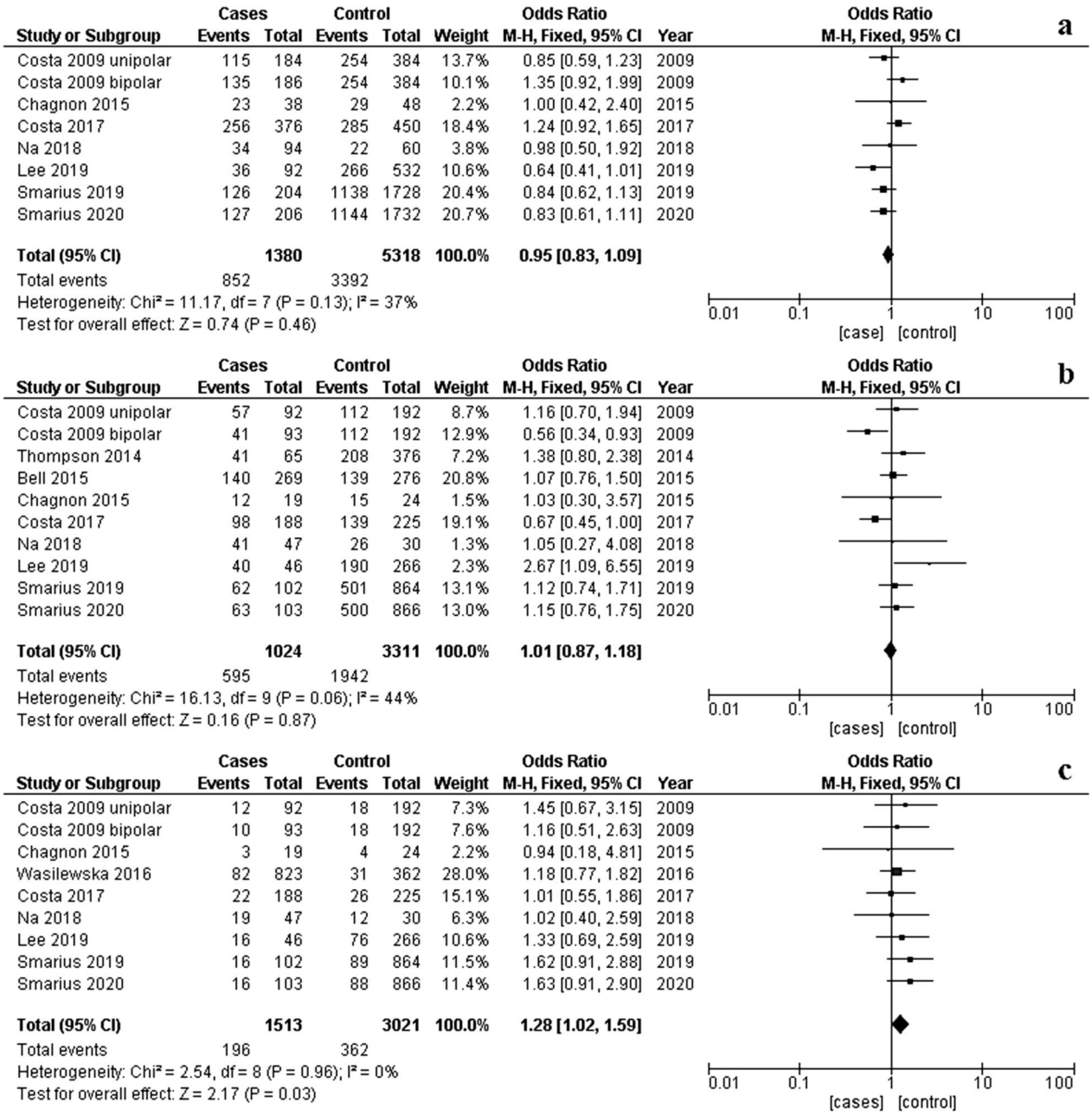


**Fig. 2** Forest plot of the association between OXTR polymorphism (rs53576) and depression risk in different models: **a** Allelic, **b** Dominant, **c** Recessive

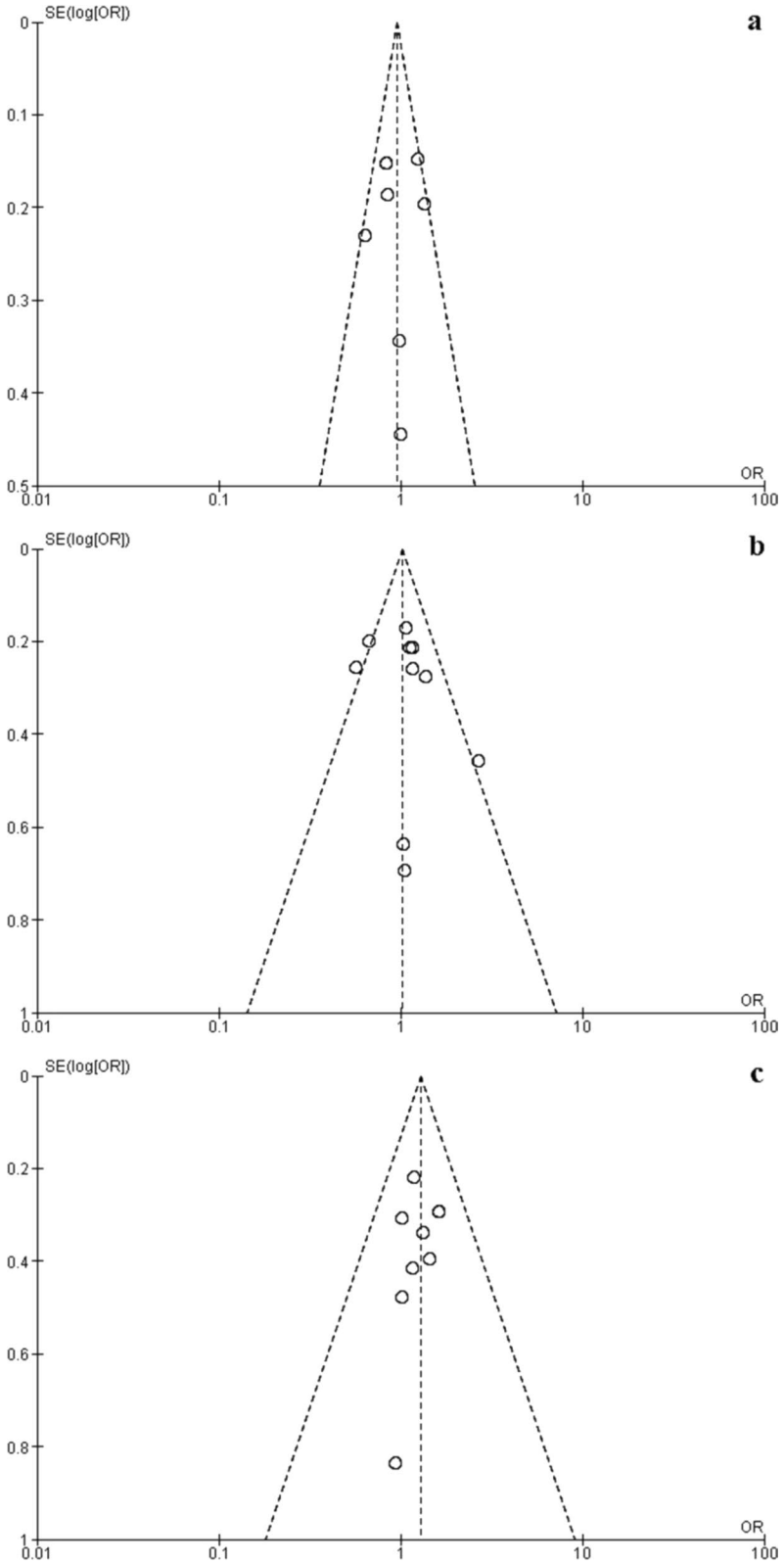


**Fig. 3** Funnel plot of the association between OXTR polymorphism (rs53576) and depression risk in different models: **a** Allelic, **b** Dominant, **c** Recessive

studied models do not show evidence of publication bias (Fig. 3).

### Subgroup analysis

In all 9 included studies in the recessive model, 7 studies were from Caucasian and 2 studies were from Asian populations. A significant association between *OXTR* polymorphism (rs53576) and depression risk is observed in the Caucasian populations (OR = 1.29, 95% CI [1.01, 1.64], $p = 0.04$) (Fig. 4a), while the Asian populations show no significant association (OR = 1.22, 95% CI [0.71, 2.09], $p = 0.48$) (Fig. 4b).

## Discussion

The association between *OXTR* gene polymorphisms and the various aspects of human disorders has gained increased interest since the discovery of *OXTR* gene structure [19]. These studies have evaluated the effect of *OXTR* gene variations on early childhood behavior, autism spectrum disorder (ASD), depression, anxiety, alcohol abuse, attention deficit hyperactivity disorder (ADHD), borderline personality disorder, and other social and emotional traits [22]. The *OXTR* SNP rs53576 (G/A) has been associated with the risk of comorbid depressive and disruptive behavior disorders [2]. The association between *OXTR* SNPs and alcohol abuse was evaluated [10]. *OXTR* rs53576 had no association with the consumption of alcohol in females, while the male A allele carriers proved to be frequent consumers [37]. The same SNP showed an interaction with childhood maltreatment in the prediction of borderline personality disorder (BPD) [9]. Hovey and colleagues showed that *OXTR* SNPs rs7632287 and rs4564970 are significantly associated with antisocial behavior in boys [18]. Several studies have examined the association between *OXTR* polymorphisms and autism spectrum disorder (ASD) and identified differences in the *OXTR* genotype between ASD cases and controls [22]. The association between *OXTR* SNPs and ADHD phenotypes was identified among children with ADHD [30]. Also, various studies have directly linked the *OXTR* SNPs with social abilities and behavior [16].

Previous meta-analyses have examined the role of *OXTR* polymorphisms in some of the above-mentioned diseases. For example, a meta-analysis was performed to evaluate the association of *OXTR* polymorphisms with antisocial behavior [31]. Another analysis studied the impact of *OXTR* rs53576 on empathy [14]. In addition, Li and colleagues performed a meta-analysis and found a positive association between *OXTR* rs53576 and general sociality [24].

In the current meta-analysis, we used data from 10 studies, including 1847 cases and 3673 controls, and found a significant association of *OXTR* SNP rs53576 (G/A) with depression in the recessive model, with no association in dominant or allelic models. This suggests that the existence of one (A) allele is not enough to alter the depression risk. According to the meta-analysis results, only people with homozygote genotype (AA) are more susceptible to developing depressive symptoms in their lives. This result is

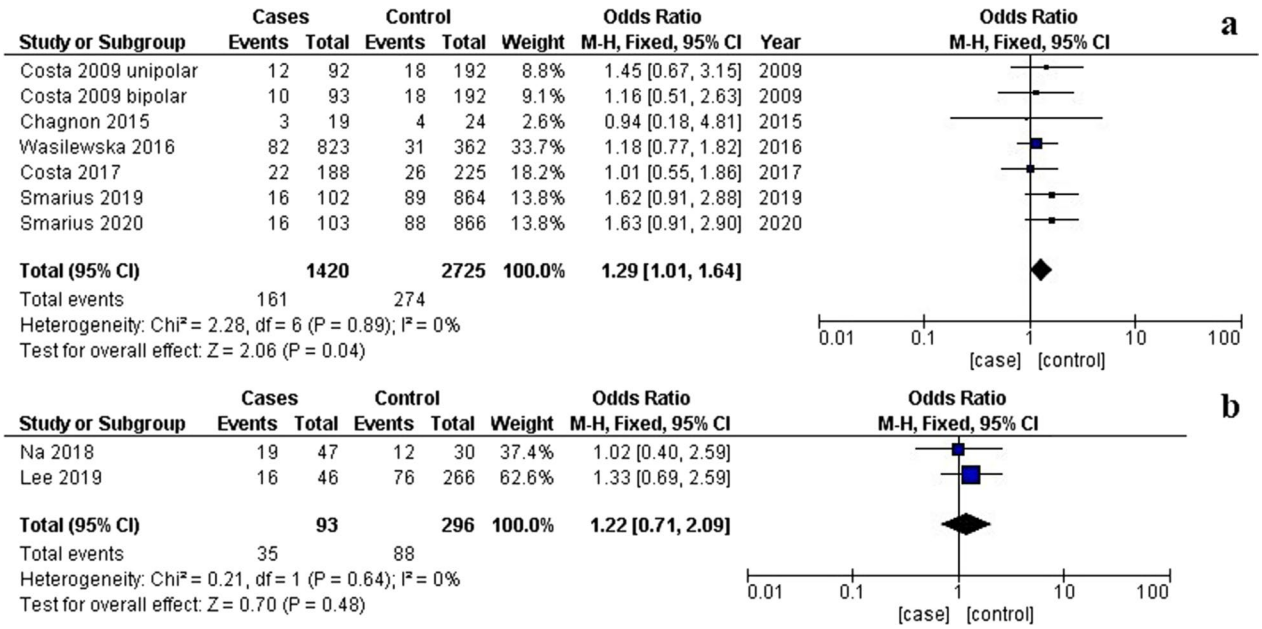


**Fig. 4** Forest plot of the association between OXTR polymorphism (rs53576) and depression risk in different populations: **a** Caucasian, **b** Asian

consistent with the findings of the previous studies that have shown associations between the SNP rs53576 and psychological traits, with most of them concluding that (A) allele carriers have an increased sensitivity to stress and negative mental health issues compared to the carriers of the homozygote GG genotype [32].

We also performed a subgroup analysis based on ethnicity and showed a significant association between the studied polymorphism and depression risk in the Caucasian population. However, the Asian subgroup has shown no such association. At this point, we should mention that the rs53576 allele frequencies significantly differ among ethnic groups. (A) allele is a minor allele for Europeans, while it's the opposite for East Asians. This indicates the importance of ethnic homogeneity regarding this polymorphism [40].

This meta-analysis had several strengths. To the best of our knowledge, this meta-analysis is the first to examine the association of *OXTR* SNP rs53576 with depression risk and to evaluate its impact in different ethnic subgroups. In addition, there was no significant heterogeneity in all the used models ($P > 0.05$). Moreover, the clear inclusion and exclusion criteria presented in this study strictly ensured the relevance of the included articles and therefore reduced selection bias.

However, several limitations should be mentioned. The number of included studies is considered relatively low, which means that the obtained results reflect the current available data from the literature and can serve as a guide for further research without necessarily providing definitive facts about the impact of the studied SNP. Furthermore, the authors of some of the included articles had conducted their research on a small sample size [7, 29], and having a proper sample size is crucial to avoiding false negative results [17]. In addition, the mechanisms related to oxytocin are sex-dependent [13] and the proportion between males and females should be balanced.

Recently emerging data indicates that the COVID-19 outbreak caused a global significant increase in the prevalence of mental health disorders, including depression and anxiety, due to the governmental implemented measures of self-isolation and social distancing [20, 25]. Scientists suggested that oxytocin could be a strong candidate to relieve social stress amid the pandemic, based on its role in promoting homeostasis, suppressing inflammation, and accelerating damage repair [39]. This draws attention to the importance of studying the association of *OXTR* SNPs with other diseases, such as COVID-19 and other infections' severity, besides focusing solely on their impact on the psychological disorders.

## Conclusion

The performed meta-analysis indicated an overall association of *OXTR* SNP rs53576 with increased depression risk in the recessive model of inheritance. Further subgroup analysis confirmed this association in Caucasians, while it was not significant in Asian populations. This suggests that the studied polymorphism has an ethnicity-dependent effect. Considering the diversity of the included studies in terms of sample size, gender balance, and ethnicity, further research is needed to better understand the effect of *OXTR* rs53576 on depression risk.

### Abbreviations

| | |
|---|---|
| OR | Odds ratio |
| CI | Confidence interval |
| SNP | Single nucleotide polymorphism |
| OXT | Oxytocin |
| OXTR | Oxytocin receptor |
| GPCR | G-protein coupled receptor |
| MDD | Major depressive disorder |
| ASD | Autism spectrum disorder |
| ADHD | Attention deficit hyperactivity disorder |

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### Author contributions

ME: Study design. ME, ED, and EB: Search for articles, data extraction from the included studies, and performing meta-analysis. ME: Writing- original draft. ED and EB: Writing-review and editing. All authors read and approved the final manuscript.

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### Availability of data and materials

Authors confirm that the data supporting the study findings are available within the article.

## Declarations

### Ethics approval and consent to participate

Not Applicable.

### Consent for publication

Not Applicable.

### Competing interests

The authors declare that they have no competing interests.

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## Publisher's Note