ASSOCIATION BETWEEN THE GENETIC VARIATIONS IN *ADAM12* AND THE SUSCEPTIBILITY TO KNEE OSTEOARTHRITIS: AN UPDATED META ANALYSIS

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ABSTRACT

Various studies have reported that genetic variations in *ADAM12* (a disintegrin and metalloprotease 12) gene lead to the development of the most common joint disorder Knee osteoarthritis (KOA). However, the studies' outcomes are conflicting**.** Therefore, the relationships between the genetic variations and KOA risk were analyzed through the current meta-analysis. Following the comprehensive literature search, odds ratios (ORs) and 95% confidence intervals (CIs) were computed for the influence of *ADAM12* polymorphisms in conferring KOA susceptibility. A total of eleven research articles, comprised of 7012 controls and 5180 cases, were found eligible for the final evaluation. The *ADAM12-rs1871054* showed a significant association with the susceptibility to KOA under the dominant (OR 1.55, 95% CI 1.19–2.02, $P = 0.001$) and additive (OR 1.71, 95% CI 1.03–2.85, $P = 0.04$) models. The *ADAM12-rs3740199* showed a positive association with the OA susceptibility under the dominant (OR 2.67, 95% CI 1.16–6.14, $P = 0.02$) and recessive (OR 0.28, 95% CI 0.14–0.59, $P < 0.001$) models in males. However, the *rs1044122* and *rs1278279* showed no associations with the OA predisposition in any of the genetic models. Hence, the current meta-analysis suggests that *ADAM12-rs1871054* and *rs3740199* have a significant association with KOA susceptibility.

Keywords Osteoarthritis. *ADAM12*. Polymorphism. SNP. Genotyping. Meta-analysis

INTRODUCTION

Osteoarthritis (OA) is the most prevalent degenerative joint disorder and the leading source of Years Lived with Disabilities (YLDs) across the globe (Vos *et al.,* 2015). Approximately 250 million people have been reported worldwide, suffering from OA, which represented 3.6% of the population (Vos *et al.,* 2012). OA prevalence has been increasing significantly over the past 20 years and is likely to be increased further (Holt *et al.,* 2011; Turkiewicz *et al.,* 2015). Moreover, OA occurrence has also been increased among younger people (Leskinen *et al.,* 12; Yu *et al.,* 2015). Knee OA (KOA) is the most common disorder with a gradual progression leading to disability. However, about 3.4% of the patients develop the accelerated OA in 4 years (Driban *et al.,* 2014; Driban *et al.,* 2020). The joint disorder occurs by the articular cartilage degradation as a consequence of bone-on-bone friction in the joints area that causes pain and stiffness with movement limitations. Various risk factors, including age, female sex, excessive joint use, and obesity, contribute to OA development, and approximately 30% of OA risk is genetically determined (Valdes *et al.,* 2010). Several Genome-Wide Association Studies (GWAS) have stated that various single nucleotide polymorphisms (SNPs) showed an association with the reduced thickness of articular cartilage in the patients suffering from KOA and hip OA (Casalone *et al.,* 2018; Styrkarsdottir *et al.,* 2017).

A disintegrin and metalloprotease 12 (*ADAM12*) gene is a member of the *ADAM* family, which is one of the candidates associated with OA susceptibility (Wu *et al.,* 2017). The *ADAM* family comprises more than 30 zinc-dependent proteases that are accountable for proteolytic activities, adhesion, and intracellular signaling (Giebeler and Zigrino, 2016). Similarly, the *ADAM12* gene is responsible for the development of bones, proliferation of chondrocytes, and differentiation of osteoclasts while playing a very critical role in both normal physiology and OA pathology (Okada, 2008). Therefore, the genetic investigations of the *ADAM12* were carried out in various OA-centered studies encompassing diverse ethnic groups and populations (Hao *et al.,* 2017; Poonpet *et al.,* 2016). The extracellular matrix (ECM) of cartilage is well-maintained through the proliferation of chondrocytes. Under normal physiological conditions, chondrocytes uphold the balance between the development and deterioration of cartilage ECM, ensuring articular cartilage maintenance. In the case of *ADAM12* genetic alterations, the equilibrium shifts towards the excessive degradation of cartilage through the overexpression of *ADAM12* gene-encoded matrix-metalloproteinase, which leads to cartilage loss and OA (Okada *et al.,* 2008; Roy *et al.,* 2004). In addition, the *ADAM12* gene may contribute to the arthritis predisposition through osteophytosis that is related to bone remodeling and neochondrogenesis (Kerna *et al.,* 2013). Osteophytes act as an indicator of the remodeling processes and reflect OA progression in affected joints. The *rs1044122* represents synonymous polymorphism in

the *ADAM12* gene, which showed a significant association with osteophytosis, predominantly in female cases of OA (Kerna *et al.,* 2013). Besides, the intronic variant *rs1871054* may elevate the *ADAM12* gene translation in bones and joints with progressive cartilage ECM degeneration (Lv *et al.,* 2017). Though various studies have evaluated the relationship between these SNPs of the *ADAM12* gene and the proneness to KOA in multiple ethnic groups, the obtained results are varying among the studied populations. The *rs1044122* has not shown any association with OA susceptibility in various studies (Jung *et al.,* 2019; Lou *et al.,* 2014; Valdes *et al.,* 2006; Wang *et al.,* 2015). Similarly, the synonymous substitution *rs1278279* and missense polymorphism *rs3740199* in the *ADAM12* gene showed no relationship to KOA predisposition in the previous studies (Hu *et al.,* 2017; Jung *et al.,* 2019; Kerna *et al.,* 2013; Lou *et al.,* 2014; Lv *et al.,* 2017; Valdes *et al.,* 2006; Wang *et al.,* 2015). The association of *rs1871054* was also not observed in the Caucasian population (Valdes *et al.,* 2006). However, a meta-analysis confirmed the substantial contribution of *rs1871054* to KOA exposure (Lv *et al.,* 2017). In addition, a meta-analysis based on 6848 controls and 5048 OA cases suggested that the *rs1044122* and *rs1871054* might have a strong association with the vulnerability to OA (Hu *et al.,* 2017). Hence, *ADAM12* gene polymorphisms are likely to be involved in developing OA through the excessive degeneration of articular cartilage and osteophytes development. Unfortunately, no consensus has yet reached on these associations. Therefore, the meta-analysis aimed to critically review the reported data and estimate the *ADAM12* polymorphisms' relationship to KOA exposure. The association analyses of the *ADAM12* gene polymorphisms with OA predisposition would provide an insight into OA research.

MATERIALS AND METHODS

Database search

According to the specifications to report the meta-analyses based on observational studies in epidemiology (Stroup *et al.,* 2000), a systematic search of the studies was carried-out employing Google Scholar and PubMed till October 2020. The words "ADAM12" AND "osteoarthritis" AND "polymorphism" AND "*rs3740199*" OR "variant" OR "*rs1044122*" OR "*rs1278279*" OR "*rs1871054*" were searched to retrieve the studies.

Exclusion and inclusion criteria

The articles were included if (1) The study revealed the relationship between the *ADAM12* SNPs and OA susceptibility. (2) The literature reported the odds ratio (OR) and 95% confidence interval (CI) for any of the four *ADAM12* polymorphisms (*rs1044122, rs1278279, rs1871054,* and *rs3740199*). However, abstracts, meta-analyses, reviews, or case reports-based studies were excluded-out.

Data isolation

For a common consensus, two researchers independently extracted the data from each of the included study, including the name of the first author, publication year, participants' countries and ethnicities, employed genotyping protocols, frequency of the controls and cases, genotypic and allelic distribution, risk of KOA conferred by the variant genotype or allele under four models of inheritance.

Statistical Investigations

All statistical analyses employed the STATA 12.0 and RevMan 5.4 software. The associations between the *ADAM12* polymorphisms, and KOA exposure, were estimated through the OR with 95% CI. The pooled-OR was computed, under four models of inheritance, including the dominant (TT vs. TC + CC or GG vs. GA + AA or GG vs. GC + CC), recessive (TT + TC vs. CC or GG + GA vs. AA or GG + GC vs. CC), additive (TT vs. CC or GG vs. AA or GG vs. CC), and allelic (T vs. C or G vs. A or G vs. C) models. The statistical significance of the association was estimated through the *Z*-test. The heterogeneity among the incorporated studies was checked by Cochran's *Q*-test, with the *P*-value (< 0.10) considered statistically significant (Cao *et al.,* 2015). In cases of insignificant heterogeneity, the fixed-effects models were employed (Mantel and Haenszel, 1959). In the case of statistically significant heterogeneity, the random-effects model was used (DerSimonian and Laird, 1986). The *I*-squared test was employed to quantify the heterogeneity with I^2 (> 50%) revealed considerable heterogeneity (Higgins *et al.,* 2003). For visualizing the overall effect of each analysis, forest plots were drawn. Begg's funnel plots were employed to estimate the publication bias (Egger *et al.,* 1997). The control participants of each of the included studies were checked for the Hardy-Weinberg equilibrium (HWE) employing the Chi-squared test. $P < 0.05$ was considered statistically significant.

RESULTS

Features of the included studies

The initial database search generated 433 studies. Removal of the duplicates excluded 186 articles. After a thorough review and detailed investigation of each full-text article, 11 of them matched the inclusion criteria of the present meta-analysis, as shown in Fig. **1**. The retrieved studies comprised a total of 7012 controls and 5180 cases (Aguilar Muñiz *et al.,* 2020; Kerna *et al.,* 2009; Kerna *et al.,* 2013; Limer *et al.,* 2009; Lou *et al.,* 2014; Poonpet *et al.,* 2016; Rodriguez-Lopez *et al.,* 2009; Shin *et al.,* 2012; Valdes *et al.,* 2004; Valdes *et al.,* 2006; Wang *et al.,* 2015). The baseline features of the included studies are summarized in Table 1.

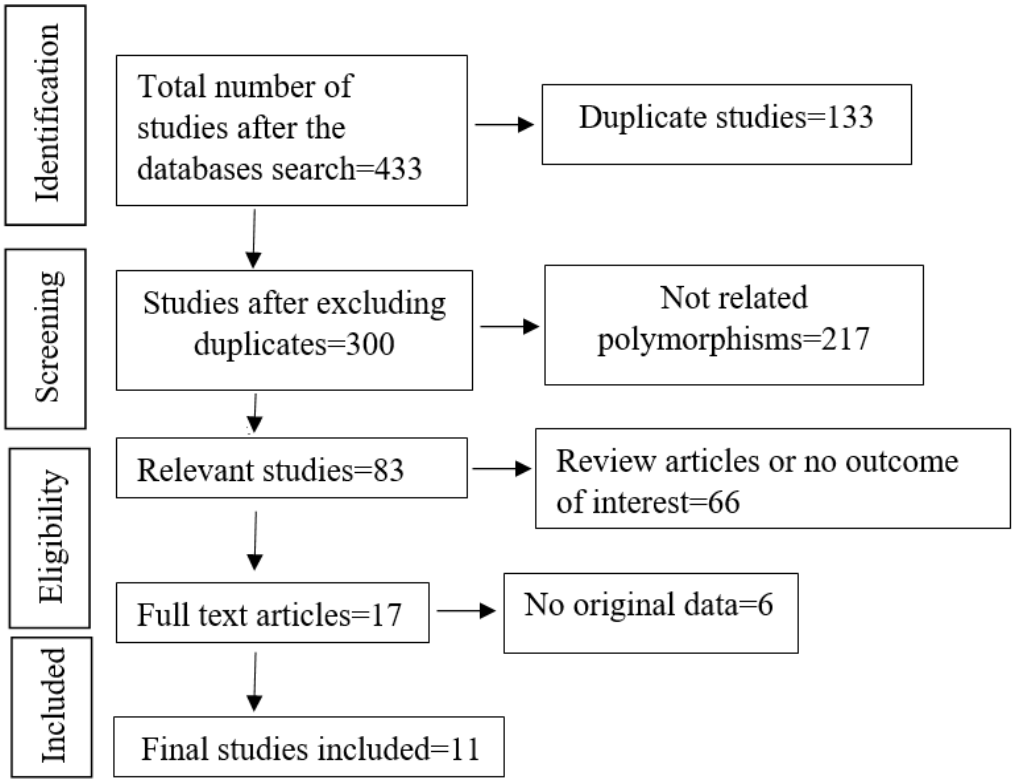

Fig.1 Flow-chart for the selection of studies.

Association between *ADAM12* SNPs and the susceptibility to OA

The genotype distribution of controls in each of the included study was consistent with the HWE, as shown in Table 2. The estimated associations between the *ADAM12* SNPs (*rs1044122*, *rs1278279*, *rs1871054*, and *rs3740199*) and KOA exposure are provided in Table 3. A total of four studies consisting of 1184 controls, and 1104 cases, were included for the *ADAM12-rs1044122*. However, an insignificant association between the *ADAM12* SNP, and KOA susceptibility, was observed under each of the currently studied model of inheritance. Similarly, for the *ADAM12-rs1278279*, a total of three studies involving 975 controls and 919 cases also showed an insignificant association between the polymorphism and KOA risk under every genetic model of the present study. Besides, six studies comprised of 1282 controls and 1168 KOA patients showed a positive relationship of the *ADAM12-rs1871054* to the disease susceptibility under the dominant (OR 1.55, 95% CI 1.19–2.02, P = 0.001) and additive (OR 1.71, 95% CI 1.03–2.85, P = 0.04) models. The *rs1871054* also showed a significant association with the OA susceptibility under the allelic model (OR 1.83, 95% CI 1.03−3.26, P = 0.04) in males. The forest plots of *ADAM12-rs1871054* and KOA susceptibility under various models of inheritance are shown in Fig. **2**.

In the case of *ADAM12-rs3740199*, a total of ten studies comprised of 6799 controls and 4955 cases reported the KOA exposure conferred by the polymorphism. Pooling the OR from the included studies revealed no relationship between the SNP and KOA exposure in the studied genetic models. However, the data stratified analyses based on gender showed a significant association between the *rs3740199* and OA susceptibility under the

dominant (OR 2.67, 95% CI 1.16–6.14, $P = 0.02$) and recessive (OR 0.28, 95% CI 0.14–0.59, $P < 0.001$) models, in males.

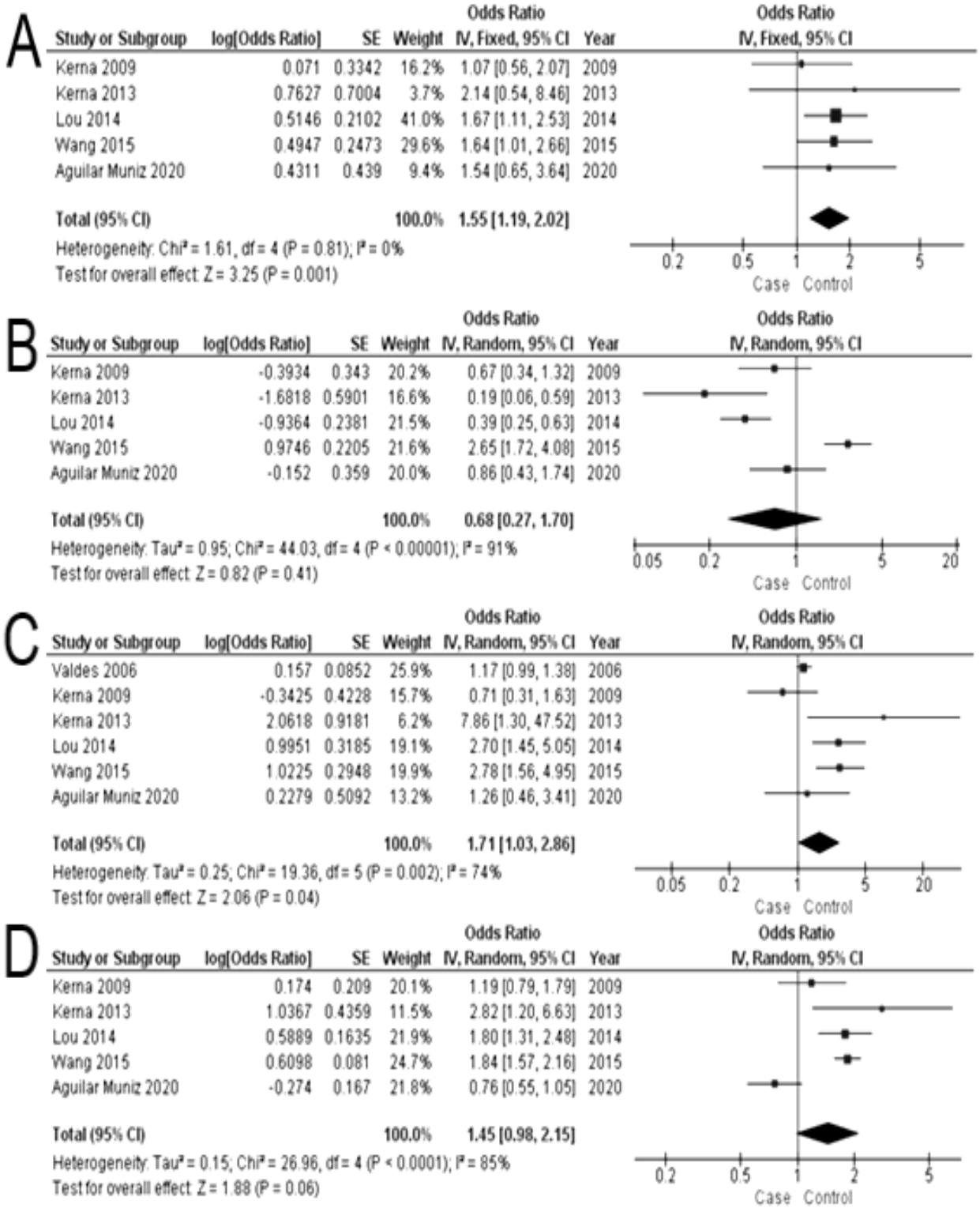

Fig. 2. Forest plots of *ADAM12-rs1871054* and knee osteoarthritis susceptibility. **a** dominant, **b** recessive, **c** additive, **d** allelic models. CI: Confidence interval.

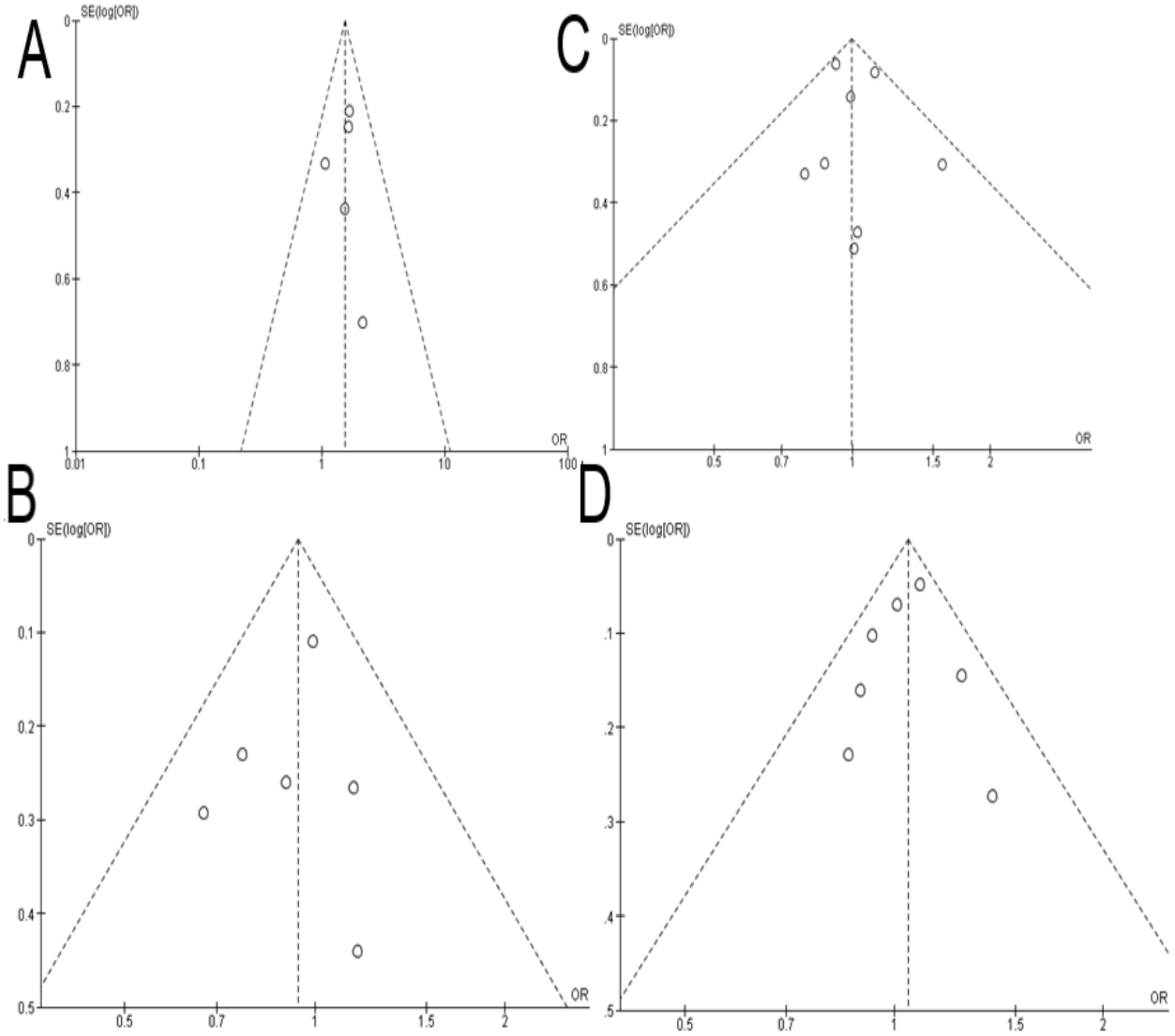

Fig. 3. Funnel plots for the OA and *ADAM12* polymorphisms. **a** dominant model of *rs1871054*, **b** recessive model of *rs3740199*, **c** additive model of *rs3740199*, **d** allelic model of *rs3740199*.

SE: Standard error; OR: Odds ratio

Heterogeneity analyses

The present meta-regression analyses exhibited a significant heterogeneity for the *rs1044122* under the dominant (TT vs. TC + CC $P = 0.06$) and additive (TT vs. CC $P = 0.08$) models. Similarly, for *rs1871054*, significant heterogeneity was observed under the recessive (TT + TC vs. CC $P < 0.001$), additive (TT vs. CC $P = 0.001$), and allelic (T vs. C $P < 0.001$) genetic models. Moreover, the data stratified analyses showed a significant heterogeneity for *rs1871054* under the recessive and additive genotypic models ($P < 0.001$) in males. The current investigation also revealed the considerable heterogeneity for *rs3740199* under the dominant genetic model (GG vs. GC + CC $P = 0.08$). Besides, the *ADAM12-rs3740199* showed a significant heterogeneity under the dominant model ($P = 0.04$) in females and the additive and allelic models ($P < 0.001$) in males.

Sensitivity test

For evaluating the individual effect of each study, the sensitivity of this study was tested by the successive exclusion of each included study. The pooled ORs were not perceived to be considerably affected that reveal the strength and reliability of the observed outcomes.

Table 1. Baseline features of the included research articles.

Study	Year	Country	Ethnicity	Method	Sample size	Control/Case	SNP
Valdes *et al*.	2004	UK	European	PCR–SSCP	749	469/280	*rs3740199*
Valdes *et al*.	2006	UK	European	Multiplex PCR	1199	596/603	*rs1044122, rs1278279, rs1871054, rs3740199*
Kerna *et al.*	2009	Estonian	European	PCR–RFLP	189	92/97	*rs1871054, rs3740199*
Limer *et al*.	2009	UK	European	TaqMan	1832	792/1040	*rs3740199*
Rodriguez-Lopez *et al*.	2009	Multinational	European	Multiplex– PCR	3932	2370/1562	*rs3740199*
Shin *et al.*	2012	Korean	Asian	TaqMan	2462	1737/725	*rs3740199*
Kerna *et al*.	2013	Estonian	European	TaqMan	438	213/225	*rs1044122, rs1871054*
Lou *et al.*	2014	China	Asian	TaqMan	331	179/152	*rs1044122, rs1278279, rs1871054, rs3740199*
Wang *et al.*	2015	China	Asian	iMLDR	364	200/164	*rs1044122, rs1278279, rs1871054, rs3740199*
Poonpet *et al*.	2016	Thai	Asian	HRM–SNP	400	200/200	*rs3740199*
Aguilar Muniz *et al*.	2020	Mexico	Mexican Mestizo	TaqMan	296	164/132	*rs1871054, rs3740199*

Table 2. Genotype frequencies of the *ADAM12* polymorphisms reported in the included studies.

Study	Year	Control			Case			HWE
rs1044122		TT	TC	CC	TT	TC	CC	
Valdes *et al*.	2006	NA	NA	NA	NA	NA	NA	> 0.10
Lou *et al*.	2014	56	92	31	47	81	24	0.51
Wang *et al.*	2015	62	101	37	51	88	25	0.71
Kerna *et al.*	2013	GG 34	GA 93	AA 82	GG 14	GA 92	AA 79	0.38
rs1278279		GG	GA	AA	GG	GA	AA	
Valdes *et al.*	2006	NA	NA	NA	NA	NA	NA	> 0.10
Lou *et al.*	2014	106	60	13	84	59	9	0.27
Wang *et al.*	2015	121	64	15	92	62	10	0.11
rs1871054		TT	TC	CC	TT	TC	CC	
Valdes *et al.*	2006	NA	NA	NA	NA	NA	NA	> 0.10
Kerna *et al.*	2009	24	49	19	24	46	27	0.51
Kerna *et al.*	2013	14	29	08	03	07	10	0.27
Lou *et al.*	2014	47	88	44	26	57	69	0.82
Wang et al.	2015	52	99	49	29	59	76	0.89
Aguilar Muniz *et al.*	2020	21	90	53	24	76	32	0.07
rs3740199		GG	GC	CC	GG	GC	CC	
Valdes *et al*.	2004	NA	NA	NA	NA	NA	NA	0.45
Valdes *et al*.	2006	NA	NA	NA	NA	NA	NA	> 0.10
Kerna *et al*.	2009	08	43	41	10	34	53	0.48
Rodriguez-Lopez *et al*.	2009	NA	NA	NA	NA	NA	NA	> 0.05
Limer *et al*.	2009	NA	NA	NA	NA	NA	NA	0.587
Shin *et al.*	2012	524	863	350	214	364	147	0.87
Lou *et al*.	2014	44	93	42	42	78	32	0.60
Wang *et al*.	2015	51	102	47	44	84	36	0.77
Poonpet *et al*.	2016	54	100	46	42	102	56	0.98
Aguilar Muniz *et al*.	2020	67	76	21	58	45	29	0.93

A: not available; HWE: Hardy-Weinberg equilibrium

Table 3. Analysis of the association between the *ADAM12* SNPs and knee OA susceptibility.

Polymorphism	No. of Studies	Control/Case	OR (95% CI)	*P*	Effect Model	$P_{heterogeneity}$	I^2 (%)
rs1044122							
TT vs. TC + CC (dominant)	3	588/501	1.24 (0.75–2.05)	0.41	Random	**0.06**	66
TT + TC vs. CC (recessive)	3	588/501	0.89 (0.67–1.18)	0.41	Fixed	0.63	0
TT vs. CC (additive)	4	1184/1104	1.06 (0.72–1.55)	0.78	Random	**0.08**	55
T vs. C (allele)	3	588/501	1.05 (0.89–1.24)	0.58	Fixed	0.12	53
rs1278279							
GG vs. GA + AA (dominant)	2	379/316	1.15 (0.86–1.55)	0.35	Fixed	0.9	0
GG + GA vs. AA (recessive)	2	379/316	1.01 (0.55–1.87)	0.97	Fixed	0.52	0
GG vs. AA (additive)	3	975/919	1.03 (0.86–1.24)	0.71	Fixed	0.86	0
G vs. A (allele)	2	379/316	1.06 (0.89–1.26)	0.54	Fixed	0.94	0
rs1871054							
TT vs. TC + CC (dominant)	5	686/565	1.55 (1.19–2.02)	**0.001**	Fixed	0.81	0
TT vs. TC + CC (male)	2	76/45	1.41 (0.56- 3.52)	0.47	Fixed	0.42	0
TT + TC vs. CC (recessive)	5	686/565	0.68 (0.27–1.7)	0.41	Random	**< 0.001**	91
TT + TC vs. CC (male)	2	76/45	0.60 (0.06- 6.25)	0.67	Random	**< 0.001**	85
TT vs. CC (additive)	6	1282/1168	1.71 (1.03–2.85)	**0.04**	Random	**0.001**	75
TT vs. CC (female)	2	363/377	1.10 (0.88- 1.37)	0.42	Fixed	0.42	0
TT vs. CC (male)	3	376/343	1.55 (0.52- 4.63)	0.43	Random	**0.09**	59
T vs. C (allele)	5	686/565	1.45 (0.98–2.15)	0.06	Random	**< 0.001**	85
T vs. C (male)	2	76/45	1.83 (1.03- 3.26)	**0.04**	Fixed	0.18	45
rs3740199							
GG vs. GC + CC (dominant)	7	3041/1750	1.09 (0.86–1.37)	0.49	Random	**0.08**	47
GG vs. GC + CC (female)	3	685/499	1.14 (0.57–2.26)	0.72	Random	**0.04**	70
GG vs. GC + CC (male)	2	76/78	2.67 (1.16–6.14)	**0.02**	Fixed	0.44	0
GG + GC vs. CC (recessive)	6	2572/1470	0.94 (0.8–1.1)	0.45	Fixed	0.66	0
GG + GC vs. CC (female)	2	216/219	1.00 (0.66–1.51)	1.00	Fixed	0.92	0
GG + GC vs. CC (male)	2	76/78	0.28 (0.14–0.59)	**< 0.001**	Fixed	0.59	0
GG vs. CC (additive)	8	5538/3635	0.99 (0.91–1.09)	0.89	Fixed	0.50	0
GG vs. CC (female)	4	1728/1616	0.97 (0.84–1.12)	0.66	Fixed	0.26	26
GG vs. CC (male)	4	1530/846	1.24 (0.79–1.94)	0.35	Random	**< 0.001**	75
G vs. C (allele)	7	3364/2510	1.05 (0.98–1.12)	0.18	Fixed	0.46	0
G vs. C (female)	2	216/219	1.09 (0.83- 1.44)	0.53	Fixed	0.57	0
G vs. C (male)	2	76/78	0.86 (0.14–5.24)	0.87	Random	**< 0.001**	92

OR: Odds ratio, CI: Confidence interval

Publication bias

The potential publication bias was analyzed employing the funnel plots, as shown in Fig. **3**. These plots were found symmetrical that reveals the absence of potential publication bias among the studies.

DISCUSSION

KOA is a complicated joint disorder, contributed by multiple risk elements, including environmental factors, genetics, aging, and obesity (Khan *et al.,* 2020; Sandell, 2012). In humans, the *ADAM12* gene, the candidate for KOA susceptibility, is located at chromosome 10q26.3 and codes for ADAM12 protein that has structural and functional similarities with ADAMs (Gilpin *et al.,* 1998). There are two forms of ADAM12 protein. ADAM12-S is the small secreted form, and ADAM12-L is the long membrane-attached form. ADAM12-S peptide contains a protease, metalloprotease, disintegrin, and a cysteine-rich domain. In the long-form of ADAM12 protein, a cytoplasmic and transmembrane domain is also linked (Gilpin *et al.,* 1998). Zymogen, an inactive form of ADAM12 protein, has a prodomain preserving the metalloprotease activities in the dormant state, possibly via a cysteine switch (Loechel *et al.,* 1998). The prodomain is chemically cleaved into an active ADAM12 protein revealing the proteolytic activities in the metalloprotease domain (Loechel *et al.,* 1998; Springman *et al.,* 1990). The activated ADAM12 protein plays an essential role to cleave insulin-like growth factor binding protein 5 (IGFBP-5) inside the cartilage ECM to discharge the insulin-like growth factor 1 (IGF-1) from the IGFBP-5 complex (Okada *et al.,* 2008). The proteolytic activities of ADAM12 protein are highly susceptible to genetic variations. As a result, the lack of IGF-1, which is one of the growth factors for chondrocytes proliferation, may predispose the joint to its articular cartilage degeneration process and OA development (Poonpet *et al.,* 2016).

Since the chondrocytes maintain the equilibrium between the synthesis and degradation of cartilage ECM, the altered *ADAM12* gene in OA may enhance the cartilage degradation process by disturbing the balance (Okada *et al.,* 2008; Roy *et al.,* 2004). The probable approaches of such genetic variations to overexpress the *ADAM12* gene include the uncontrolled transcription process, translation of relative isoforms, or stabilization of the mRNAs (Pastinen *et al.,* 2006). Although the genetic variants, including synonymous and intronic polymorphisms of the *ADAM12* gene, do not change the protein composition, still the gene expression is likely to be transformed by altering the mRNA level that may change the time intervals of the overall translational process. Additionally, such genetic variations may change the translation rate or the protein maturation mechanism (Bartoszewski *et al.,* 2010; Kimchi-Sarfaty *et al.,* 2007). In this way, the genetic polymorphisms may lead to the enhanced expression of the *ADAM12* gene, which explains the increased mRNA level detected in the synovial tissues of OA patients (Kerna *et al.,* 2013).

The synonymous polymorphism *rs1044122* (c.2475T > C, p. Ala825Ala) at 21st exon of the *ADAM12* gene represents the variation of Ala→Ala at 825th amino acid residue in a single peptide of ADAM12. This polymorphism is mainly associated with osteophytes development, predominantly in females (Kerna *et al.,* 2013). In previous studies, *rs1044122* has shown a statistically significant association with KOA (Hu *et al.,* 2017; Kerna *et al.,* 2013). However, the genetic predisposition was not found in the Asian and Estonian populations (Kerna *et al.,* 2013; Lou *et al.,* 2014; Wang *et al.,* 2015). In the present study, a total of four research articles comprised of 1184 controls and 1104 cases exhibited the association between the ADAM12-*rs1044122* and OA susceptibility (Kerna *et al.,* 2013; Lou *et al.,* 2014; Valdes *et al.,* 2006; Wang *et al.,* 2015). However, on pooling the data, the KOA risk was not found, under any genetic model of *rs1044122*, similar to the Caucasian, Estonian, and Asian populations (Kerna *et al.,* 2013; Lou *et al.,* 2014; Valdes *et al.,* 2006; Wang *et al.,* 2015). The *ADAM12* polymorphism *rs1278279* (G > A) in the 14th exon represents the synonymous substitution without altering the amino acid sequence, Asn505Asn (Kerna *et al.,* 2013; Lv *et al.,* 2017). A total of three studies, based on 975 controls and 919 cases, were incorporated in the recent meta-analysis for *rs1278279* (Lou *et al.,* 2014; Valdes *et al.,* 2006; Wang *et al.,* 2015). However, the *ADAM12* polymorphism exhibited an insignificant association with the susceptibility to KOA under each of the studied genetic models. The *rs1871054* (c.1154 + 145T > C), at the 11th intron of the *ADAM12* gene, may enhance the gene expression in synovial joints leading to inflammation (Lv *et al.,* 2017). A significant association of *rs1871054* was reported in the Asians but not in the Caucasian population (Lv *et al.,* 2017). Moreover, the *rs1871054* showed a positive association with osteophytes development in the advanced OA (Kerna *et al.,* 2013). Besides, the *rs1871054* showed an insignificant association with OA in the Estonian and Caucasian populations (Kerna *et al.,* 2009; Valdes *et al.,* 2006). In the present study, *rs1871054* elevated the disease risk, in concordance with the Asian cohorts (Lou *et al.,* 2014; Wang *et al.,* 2015). The current meta-analysis revealed the *rs1871054* to be significantly associated with the susceptibility to KOA under the dominant and additive models of inheritance. The risk was also observed by the variant allele of *rs1871054* under the allelic model, in males which shows the higher disease susceptibility in males. Similarly, the variant genotype of *rs1871054* has elevated the risk

about one and a half times under the dominant genetic model, consistent with the Chinese population (Lou *et al.,* 2014). The statistically significant association of *rs1871054* with KOA under the dominant inheritance model of the current research reveals that a single copy of the altered allele may increase the KOA exposure, and both the heterozygous as well as homozygous variant genotypes of *rs1871054* may confer the disease risk (Bush and Moore, 2012; Clarke *et al.,* 2011). Moreover, a positive relationship of the *rs1871054* with nearly two times increased susceptibility to KOA under the additive model of recent investigation reveals the constant KOA risk increment for each copy of their variant allele (Bush and Moore, 2012).

Reference SNP *3740199* (c.142G > C, p. Gly48Arg) in 2nd exon of *ADAM12* denotes missense variation (Kerna *et al.,* 2009; Lv *et al.,* 2017), leading to the alteration of glycine amino acid (nonpolar) to arginine (positively charged) in the prodomain of *ADAM12* that is accountable for maturation, folding, activation, regulation, and transportation of the protein (Cao *et al.,* 2002; Loechel *et al.,* 1998). The proteolytic activities of *ADAM12* are indispensable for enhancing the bioavailability of insulin-like growth factor-1 (IGF-1) via cleaving the complex into IGF-1 and insulin-like growth factor-binding protein-5 (IGF BP-5). IGF-1, the potential growth factor, triggers chondrocytes proliferation. However, IGF-1 deficiency causes the cartilage degradation process (Okada *et al.,* 2008). Therefore, the amino acid alteration, as a consequence of *rs3740199*, interrupts the proteolytic activities of the *ADAM12* and causes insufficiency of IGF-1, leading to cartilage degeneration and KOA initiation (Poonpet *et al.,* 2016). The *rs3740199* showed a significant association with the enhanced predisposition to the development of KOA in females (Valdes *et al.,* 2004). Besides, two studies reported the increased risk of KOA conferred by the *rs3740199* in men (Kerna *et al.,* 2009; Poonpet *et al.,* 2016). In the present analyses, the *rs3740199* showed an insignificant association with KOA exposure. The outcomes of the recent meta-analysis are consistent with studies that reveal no association between the *ADAM12-rs3740199* and KOA susceptibility in various populations (Kerna *et al.,* 2013; Lou *et al.,* 2014; Shin *et al.,* 2012; Valdes *et al.,* 2006; Wang *et al.,* 2015). In contrast to the previous studies, the present data stratification based on gender showed a positive relationship between the *rs3740199* and OA susceptibility under the dominant and recessive models in males. Therefore, the study findings warrant further investigation.

The funnel plot indicated no remarkable publication bias in the current meta-analysis. Besides, various models of inheritance showed heterogeneity. It might be due to the inadequate studies included, the varying ethnicities, or the unintentional selection bias (Mao *et al.,* 2015).

The current meta-analysis has a few limitations that need consideration. The effect of the gene to gene and gene to environment relationships might have influenced the study outcomes, as these elements play a potential role in developing the OA pathogenesis. Similarly, factors including the female gender, age, and body mass index may also contribute to the disease development. Besides, the present research may be further engaged to identify other genes or variants involved in the *ADAM12* pathway that would provide an insight into the molecular mechanisms involved in OA development.

In conclusion, the present meta-analysis showed the significant association of the *ADAM12-rs1871054* with the OA predisposition. Besides, the *ADAM12-rs3740199* showed a positive relationship with the disease susceptibility in males. However, the *ADAM12* polymorphisms, including *rs1044122* and *rs1278279*, showed an insignificant relationship to KOA susceptibility. The study findings might be useful for determining the etiology of OA and recognizing the people at risk of developing KOA. The study outcomes will help in the development of KOA biomarkers for reviewing the genetic exposure to the OA. Hence, the study would be advantageous for developing better diagnostic and therapeutic interventions of KOA. However, further investigation is still required to validate the findings of the present study and to clarify whether the variants of the *ADAM12* gene predispose the joint to the processes of cartilage degeneration and KOA development.

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