Review Article
IL-13 polymorphisms rs20541 and rs1800925 in atopic dermatitis: a meta-analysis

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Abstract: IL-13 is an effector in airway inflammation remodeling and is an important cytokine involved in the IgE pathway. Increasing evidence suggests an important role for the 2 single-nucleotide polymorphisms (SNPs) of the *IL-13* gene in bronchial asthma. Our study aims to explore the association of rs20541 and rs1800925 with the susceptibility of atopic dermatitis (AD). Computer-based bibliographic databases literature searches were conducted using stringent inclusion and exclusion criteria to find case-controlled studies relevant to the association between the *IL-13* gene SNPs and AD susceptibility. Comprehensive Meta-analysis 2.0 software (CMA 2.0) was utilized for statistical analysis. A total of 273 studies were initially found, however, after screening only 9 eligible studies were enrolled in the current meta-analysis. These studies involved a total of 1,744 AD patients and 2,042 healthy controls. The results of our meta-analysis showed that both rs20541 and rs1800925 may predict AD susceptibility. A subgroup analysis based on ethnicity suggested that rs20541 in the *IL-13* gene is associated with an increased susceptibility to AD in both Asians and Caucasians populations. The subgroup analysis also demonstrated that rs1800925 is linked to AD susceptibility in Asians. Our study demonstrated that *IL-13* gene SNPs, rs20541 and rs1800925, are associated with AD susceptibility. Interestingly, our study revealed an ethnic difference in the association between rs20541 in IL-13 and the susceptibility to AD in Asians.

Keywords: Atopic dermatitis, interleukin-13, polymorphism, meta-analysis, rs20541, rs1800925, susceptibility and gene

Introduction

Atopic dermatitis (AD), also known as eczema, refers to a commonly chronic or relapsing inflammatory disorder which occurs on the skin [1]. AD is considered the first clinical manifestation of atopy and the onset of atopic march. It is also clinically classified into infancy, childhood and adolescent or adult types based on patient age and type of skin lesion [1, 2]. AD is generally characterized by an intense itch, high irritability and can eventually lead to the development of asthma or allergic rhinitis [3-5]. There is a high incidence of AD in infants, which may carry over to adolescences and adults. AD affects approximately 10~20% of children and 1~3% of adults in most western societies [6, 7]. Remarkably, the prevalence of AD has increased 2~3 fold over the last century in developed countries, but remains at lower levels in agricultural regions [8]. Although the pathogenesis of AD is still poorly understood, it has been found that factors contributing to AD mainly involve

barrier dysfunction of the skin, imbalance in the immune system and environmental factors such as exposure to livestock, household pets, unpasteurized milk, etc. [9, 10]. Recently an association between the interleukin-13 (*IL-13*) gene and AD susceptibility was identified [11, 12]. IL-13 is an effector in airway inflammation remodeling and is an important cytokine of the IgE pathway [13, 14]. IL-13 activates a variety of cells such as nerve cells, macrophages, B cells and mast cells. It is also engaged in the production of IgE, subepithelial fibrosis, mucus hypersecretion and eosinophil infiltration [15, 16]. IL-13 is a 12 Kda secreted protein of 33 amino acids in length and is produced by activated CD4 1 T-helper 2 cells and nuocytes [17]. IL-13 is a protein product encoded by the *IL13* gene located at chromosome 5q31. *IL13* and *IL-4* genes possess identical regulatory sequences in their promoter areas [18]. An increasing number of studies suggest that the 2 single-nucleotide polymorphisms (SNPs), rs20541 and rs1800925, can increase IL-13 production and
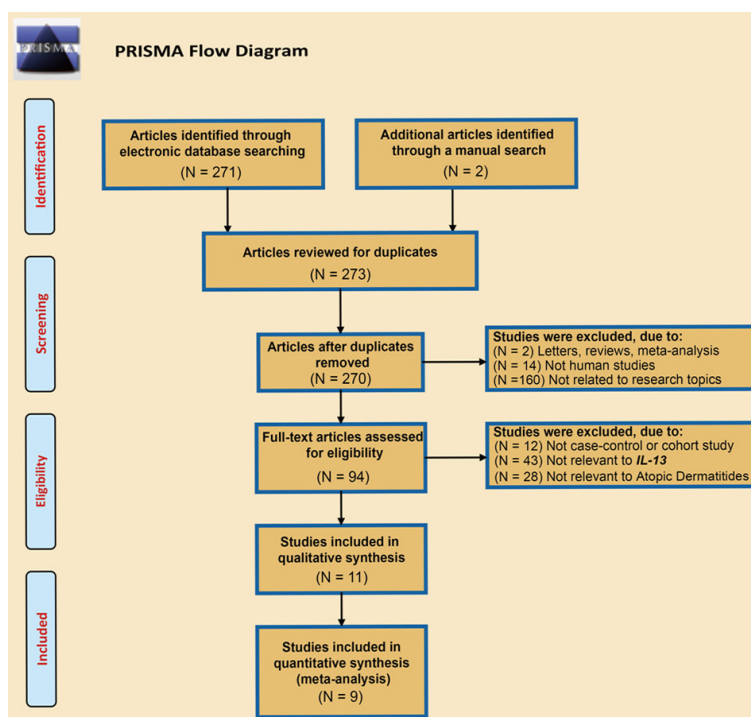
PRISMA Flow Diagram

Figure 1. Flow chart showing literature search and study selection. Nine clinical cohort studies met the inclusion criteria were included in this meta-analysis.

enhanced IL-13 promoter activities in the *IL-13* gene [19, 20]. Several studies have also indicated that these SNPs in the *IL-13* gene may have a strong link to AD susceptibility [21, 22]. On the other hand, another study suggested that rs20541 has no association with the pathogenesis of AD [23]. Given the contradictory results of previous studies, we carried out a meta-analysis to investigate the correlation between the SNPs in the *IL-13* gene and AD susceptibility.

Materials and methods

Literature search

Published studies that were relevant to the association between *IL-13* gene SNPs and AD susceptibility were identified through computerized bibliographic searches of the PubMed, Ovid, Wiley Online Library, Web of Science, Chinese Biomedical Database, Chinese Journal Full-Text, China National Knowledge Infrastructure (CNKI), Wanfang and VIP databases (from inception to Oct. 2016). Cross references from selected articles were similarly manually searched to obtain additional pertinent literature. A combination of key words and free words

("dermatitis, atopic" or "atopic dermatitides" or "dermatitides, atopic" or "neurodermatitis, atopic" or "atopic neurodermatitides" or "neurodermatitis, disseminated" or "disseminated neurodermatitides" or "eczema, atopic" or "eczema, infantile" or "prurigo constitution") and ("interleukin-13" or "IL-13" or "differentiation factor-13, B-Cell" or "B cell stimulatory factor-13") were used to identify literature in a highly efficient and sensitive search strategy.

Inclusion and exclusion criteria

Articles accord with the following criteria were included in the current meta-analysis: (1) Study themes included the association between SNPs of the *IL-13* gene and AD susceptibility; (2) Study was a case-control study; (3) Study subjects included normal healthy controls and patients with AD; (4) The end outcomes were related to allele and genotype frequency of the case-control group. The exclusion criteria were: (1) Studies which only had a summary and abstract; (2) Non-human studies; (3) Duplicated publications or grey literature; (4) Literature with incomplete data; (5) Studies which only had the largest sample size or latest study subsumed when published by the same authors/case data.

Data extraction and quality assessment

Data for meta-analysis was extracted using a unified data collection form by 2 independent investigators. The main data included the first author, publication year, ethnicity, country, age, disease, language, gender, detection method, number of cases and controls, study design and SNP. Any disagreements regarding the data were resolved via discussion by several investigators during the data extraction process. Above two researchers made quality score of included articles according to critical appraisal skill program (CASP) criteria (http://www.casp-uk.net/). The specific standards are whether the study address a clearly focused

Table 1. Baseline characteristics of the enrolled studies about rs20541 of *IL-13* gene in the meta-analysis

First author	Year	Country	Language	Ethnicity	Total	Number		Gender (M/F)		Age (years)		Genotyping methods	Gene	SNP
						Case	Control	Case	Control	Case	Control			
Liu X	2000	USA	English	Caucasians	285	187	98	-	-	-	-	PCR-SSCP	IL-13	rs20541 G>A
Tsunemi Y	2002	Japan	English	Asians	287	185	102	130/55	-	28 ± 8 (11~61)	-	PCR-RFLP	IL-13	rs20541 G>A
Chang YT	2006	China	English	Asians	280	94	186	52/42	-	27 (0~81)	-	Direct sequencing	IL-13	rs20541 G>A
Matsuda A	2007	Japan	English	Asians	360	78	282	43/35	169/113	27 (6~48)	38 (19~68)	PCR-RFLP	IL-13	rs20541 G>A
Zitnik SE	2009	Germany	English	Caucasians	1341	643	698	-	-	-	-	PCR-RFLP	IL-13	rs20541 G>A

Note: M, Male; F, Female; PCR-SSCP, Polymerase Chain Reaction-Single Strand Conformation Polymerase; PCR-RFLP, Polymerase Chain Reaction-Restriction Fragment Length Polymorphism; SNP, Polymorphism.

Table 2. Baseline characteristics of the enrolled studies about rs1800925 of *IL-13* gene in the meta-analysis

First author	Year	Country	Language	Ethnicity	Total	Number		Gender (M/F)		Age (years)		Genotyping method	Gene	SNP
						Case	Control	Case	Control	Case	Control			
Tsunemi Y	2002	Japan	English	Asians	287	185	102	130/55	-	28 ± 8 (11~61)		PCR-RFLP	IL-13	rs1800925 C>T
Hummelshoj T	2003	Denmark	English	Caucasians	159	55	104	31/24	40/64	33 (17~66)	31 (18~66)	PCR-SSP	IL-13	rs1800925 C>T
Chang YT	2006	China	English	Asians	280	94	186	52/42	-	27 (0~81)	-	Direct sequencing	IL-13	rs1800925 C>T
Zitnik SE	2009	Germany	English	Caucasians	1341	643	698	-	-	-	-	PCR-RFLP	IL-13	rs1800925 C>T
Lesiak A	2011	Poland	English	Caucasians	369	163	204	66/97	92/112	11(1~42)	-	PCR-RFLP	IL-13	rs1800925 C>T
Glen J	2012	Poland	English	Caucasians	347	180	167	-	-	(2~54)	(6~61)	PCR-ARMS	IL-13	rs1800925 C>T
Nan ML	2013	China	China	Asians	360	159	201	-	-	-	-	TaqMan assay	IL-13	rs1800925 C>T

Note: M, Male; F, Female; PCR-RFLP, Polymerase Chain Reaction-Restriction Fragment Length Polymorphism; PCR-SSP, Polymerase Chain Reaction-Sequence Specific Primer; SNP, Polymorphism; PCR-ARMS: Amplification Refractory Mutation System.

Figure 2. The CASP scores of nine included articles.

issue or not (CASPP01); whether an appropriate method was used to answer their question or not (CASP02); whether the cases were recruited in an acceptable way or not (CASP-03); whether the controls were selected in an acceptable way or not (CASP04); whether the exposure was accurately measured to minimize bias (CASP05); what confounding factors have the authors accounted for or have the authors taken account of the potential confounding factors in the design and/or in their analysis (CASP06); whether the results of this study was complete or not (CASP07); how precise are the results (CASP08); is the research credible (CASP09); can the results be applied to the local population (CASP10); do the results of this study fit with other available evidence (CASP11).

Statistical analysis

Comprehensive Meta-analysis 2.0 software (Biostat Inc., Englewood, New Jersey, USA) was utilized for statistical analysis of the extracted data. The odds ratio (OR) with 95% confidence intervals (CI) among study groups which were presented by forest plots were calculated using a fixed-effect or random-effect model to assess the differences of allele gene and gene frequency between AD patients and healthy controls. The *Z* test was used to examine the significance of the overall effect size [24]. A forest map was drawn to reflect the OR values and

95% CI of the study groups. The Cochran's Q-statistic ($P < 0.05$ was considered statistically significant) and the I^2 test (0%, no heterogeneity; 100%, maximal heterogeneity) were also applied to assess whether heterogeneity existed [25, 26]. The random-effects model was applied on evidence which was significantly heterogenic ($P < 0.05$ or I^2 test exhibited > 50%) and the fixed-effects model was utilized for non-heterogenic evidence [27, 28]. We performed a univariate meta-regression analysis to evaluate the possible source of heterogeneity and also further tested this through multivariate meta-regression analysis and multiple calibration tests which were conducted using the Monte Carlo method [25, 29]. Subsequently, a sensitivity analysis was performed to evaluate whether the removal of 1 single study would influence the overall outcomes. Furthermore, the possibility of publication bias risk was assessed using funnel plots, classic fail-safe N and the Egger's linear regression test [30, 31]. All tests were two-sided ($P < 0.05$ was considered statistically significant).

Results

Baseline characteristics of included studies

A total of 273 studies were initially identified for the current meta-analysis through electronic database and manual searches. We excluded 3 studies due to duplication, 2 studies which were letters or summaries, 14 studies which were non-human studies, 160 studies which were not related to our subject matter, 83 studies due to a lack of sufficient data and 2 studies due to low relevance of data (**Figure 1**). Finally, 9 eligible studies published between 2000 and 2013 were incorporated in our meta-analysis (**Tables 1** and **2**). The CASP scores of included articles are shown in **Figure 2**. These studies contained a total of 3786 samples (1744 AD patients and 2042 healthy controls). Our meta-analysis involved the 2 SNPs of the *IL-13* gene, rs20541 and rs1800925. Four studies were conducted on Asians (2 from
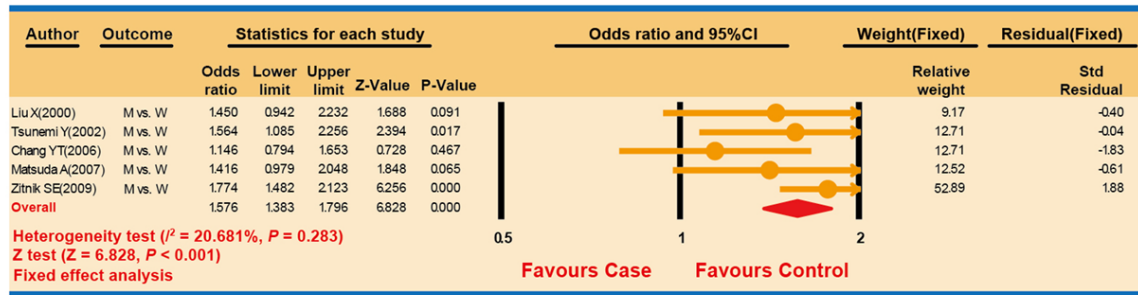
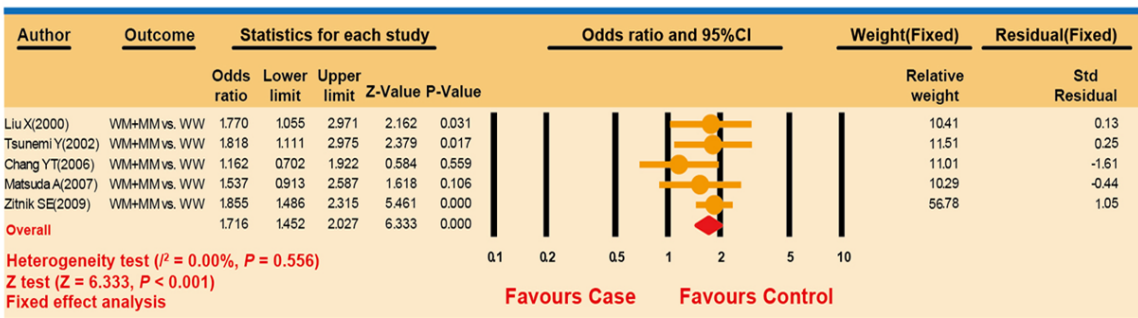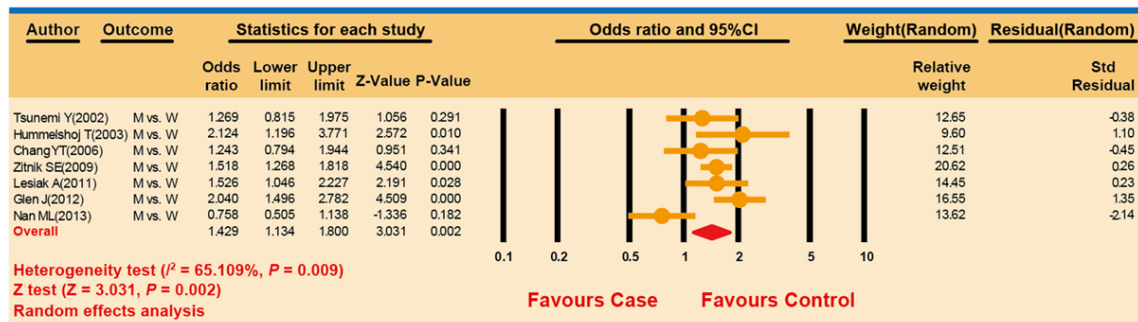**Figure 3.** Forest plots showing differences in allele gene and gene frequency of rs20541 and rs1800925 in atopic dermatitis and healthy control patients.

Japan and 2 from China) and 5 studies were conducted on Caucasians (2 from Poland, 1 from Denmark, 1 from German and 1 from America) [32-40]. Among the 9 studies, 4 studies used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and
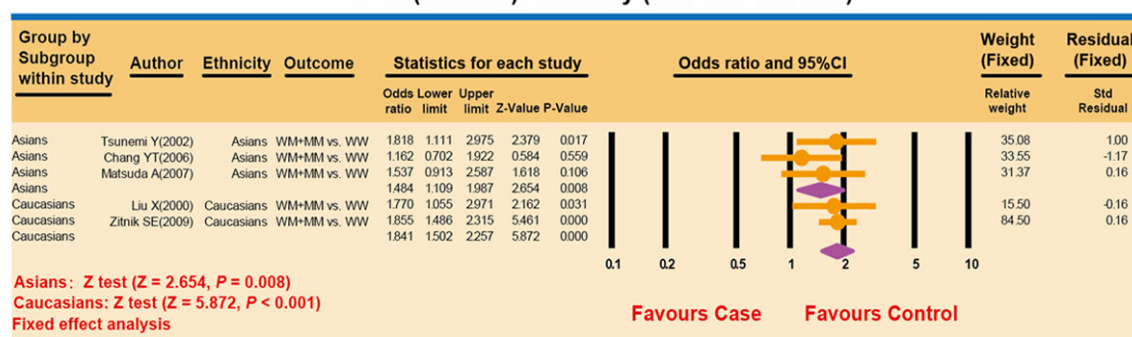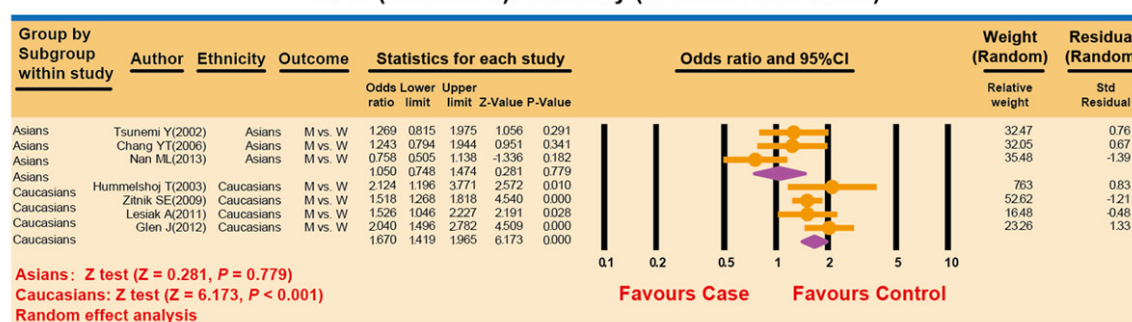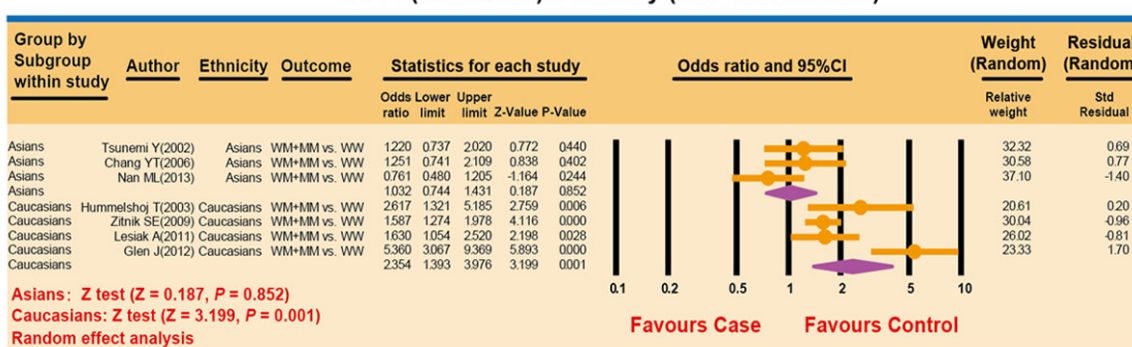
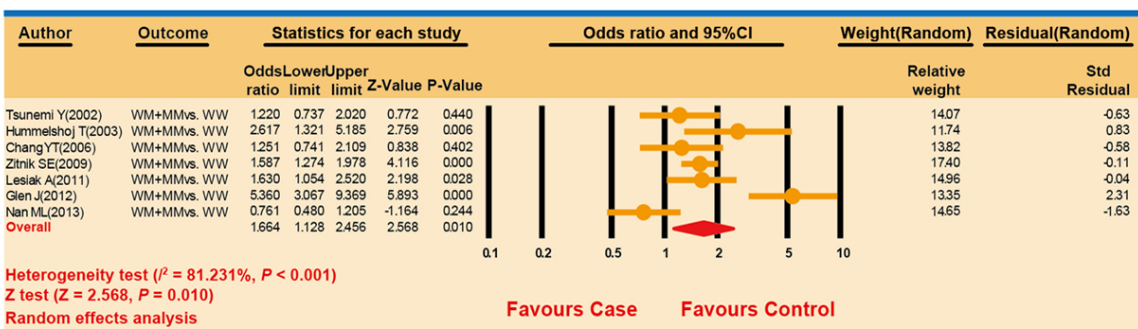**Figure 4.** Forest plots showing differences in allele gene and gene frequency of rs20541 and rs1800925 in atopic dermatitis and healthy control patients based on ethnicity.
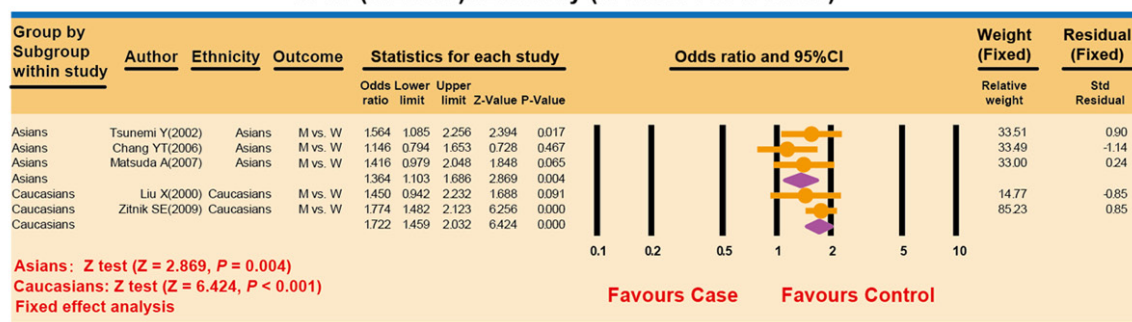
the other 5 studies used TaqMan, Direct sequencing, polymerase chain reaction-sequence specific primer (PCR-SSP), polymerase chain reaction-single strand conformation polymor-
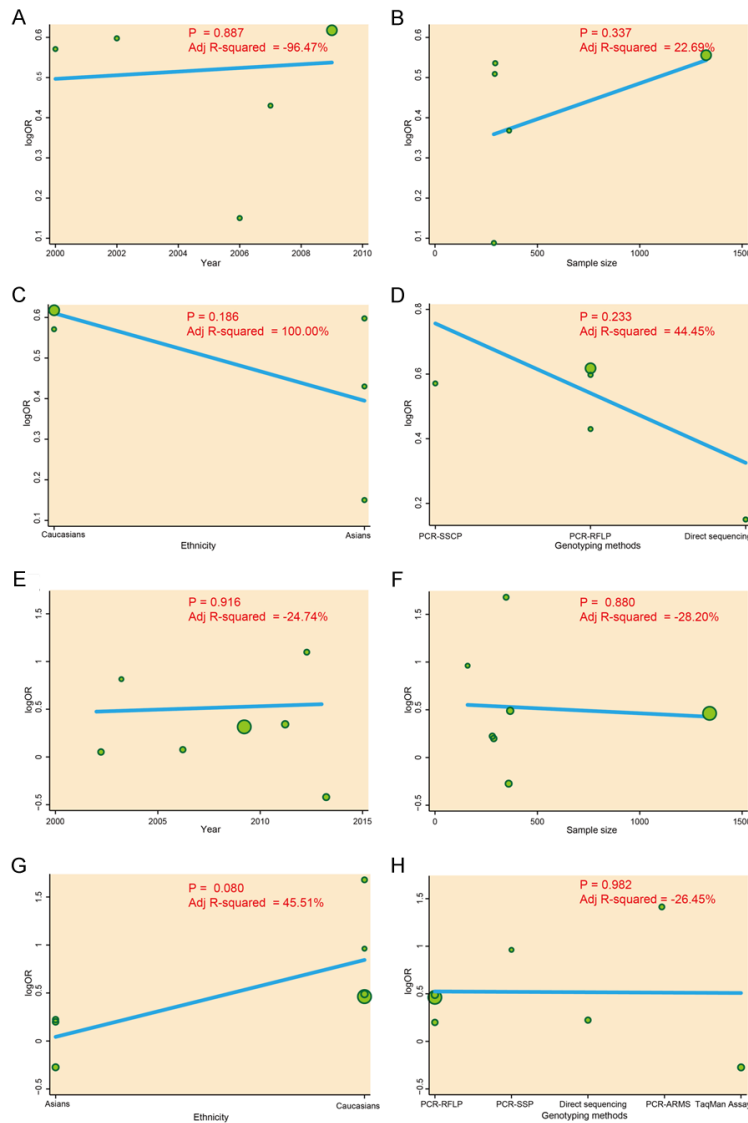
Figure 5. Univariate meta-regression analysis regarding the differences in allele gene and gene frequency of rs20541 and rs1800925 in atopic dermatitis and healthy control patients.

susceptibility, showed an absence of heterogeneity (allele model: I^2 = 20.681%, P = 0.283; dominant model: I^2 = 0.00%, P = 0.556). Therefore, the fixed effects model was applied. Results from current meta-analysis indicate that there is a close association between rs20541 and AD susceptibility. The results also demonstrated that the genetic frequency had statistical differences in the case and control groups under the allele and dominant models (allele model: OR = 1.576, 95% CI = 1.383~1.796, $P < 0.001$; dominant model: OR = 1.716, 95% CI = 1.452~2.027, $P < 0.001$) (**Figure 3A**, **3B**). The subgroup analysis based on ethnicity suggests that rs20541 can increase the susceptibility to AD in both Asians and Caucasians (Asians: allele: OR = 1.364, 95% CI = 1.103~1.686, P = 0.001; dominant: OR = 1.484, 95% CI = 1.109~1.987, P = 0.001) (Caucasians: allele: OR = 1.722, 95% CI = 1.459~2.032, $P < 0.001$; dominant: OR = 1.841, 95% CI = 1.502~2.257, $P < 0.001$) (**Figure 4A**, **4B**). The results after a single factor meta-regression analysis illustrated that heterogeneity was not correlated with publication year, ethnicity, sample size or detection method of SNP (publication year: P = 0.887; sample size: P = 0.337; ethnicity: P = 0.186; detection method: P = 0.233) (**Figure 5A-D**). Furthermore, the results after a multiple factor meta-regression analysis implied that publication year, ethnicity, sample size and detection method of SNP were not sources of heterogeneity (all $P > 0.05$).

phism (PCR-SSCP) or PCR-amplification refractory mutation system (PCR-ARMS). The studies had a sample size ranging from 159 to 1341. All genotypic distributions except rs1800925 of Tsunemi Y 2002 (P = 0.04) and Glen J 2012 used in the meta-analysis were in strict accordance with the genetics of HWE equilibrium (all $P > 0.05$).

The association between rs20541 and AD susceptibility

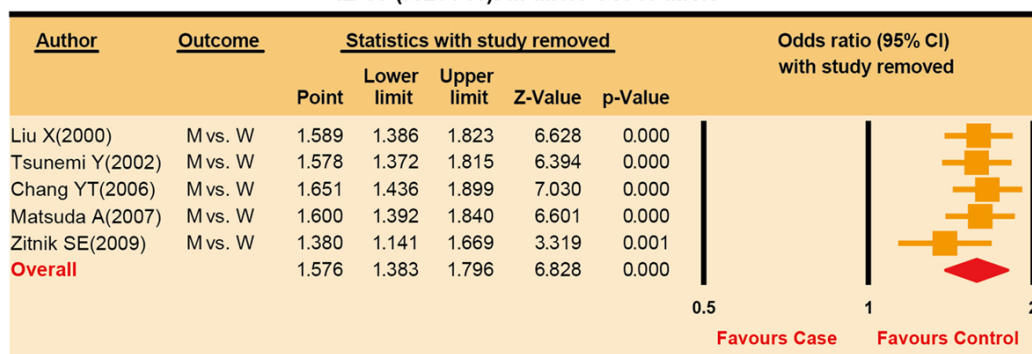Five studies, which reported an association between rs20541 SNP of *IL-13* gene and AD

The association between rs1800925 and AD susceptibility

Seven of the included studies focused on the association between rs1800925 SNPs in the

A

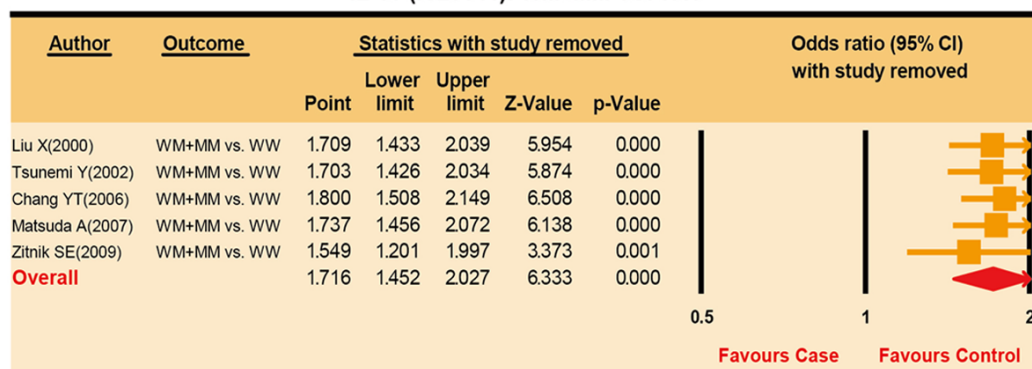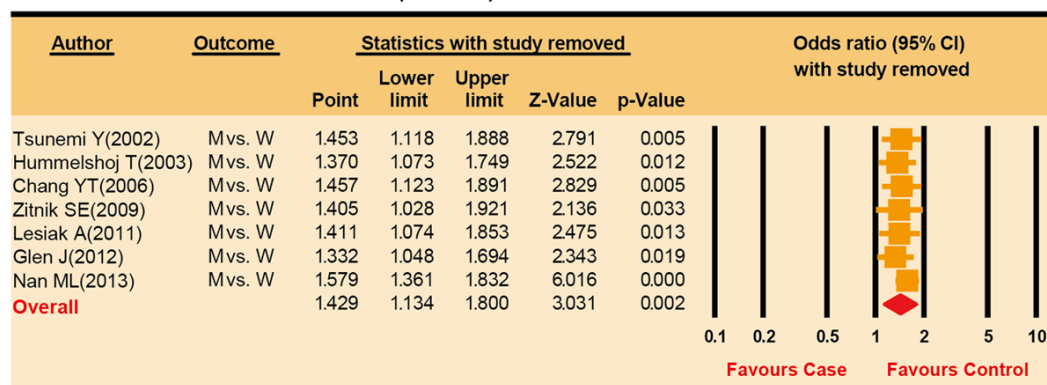### *IL-13* (rs20541): M allele VS. W allele

Author	Outcome	Point	Lower limit	Upper limit	Z-Value	p-Value	Odds ratio (95% CI) with study removed
Liu X(2000)	M vs. W	1.589	1.386	1.823	6.628	0.000	
Tsunemi Y(2002)	M vs. W	1.578	1.372	1.815	6.394	0.000	
Chang YT(2006)	M vs. W	1.651	1.436	1.899	7.030	0.000	
Matsuda A(2007)	M vs. W	1.600	1.392	1.840	6.601	0.000	
Zitnik SE(2009)	M vs. W	1.380	1.141	1.669	3.319	0.001	
Overall		1.576	1.383	1.796	6.828	0.000	

0.5   1   2
Favours Case   Favours Control

B

IL-13 (rs20541): WM+MM VS. WW

Author	Outcome	Point	Lower limit	Upper limit	Z-Value	p-Value	Odds ratio (95% CI) with study removed
Liu X(2000)	WM+MM vs. WW	1.709	1.433	2.039	5.954	0.000	
Tsunemi Y(2002)	WM+MM vs. WW	1.703	1.426	2.034	5.874	0.000	
Chang YT(2006)	WM+MM vs. WW	1.800	1.508	2.149	6.508	0.000	
Matsuda A(2007)	WM+MM vs. WW	1.737	1.456	2.072	6.138	0.000	
Zitnik SE(2009)	WM+MM vs. WW	1.549	1.201	1.997	3.373	0.001	
Overall		1.716	1.452	2.027	6.333	0.000	

0.5   1   2
Favours Case   Favours Control

C

IL-13 (rs20541): M allele VS. W allele

Author	Outcome	Point	Lower limit	Upper limit	Z-Value	p-Value	Odds ratio (95% CI) with study removed
Tsunemi Y(2002)	M vs. W	1.453	1.118	1.888	2.791	0.005	
Hummelshoj T(2003)	M vs. W	1.370	1.073	1.749	2.522	0.012	
Chang YT(2006)	M vs. W	1.457	1.123	1.891	2.829	0.005	
Zitnik SE(2009)	M vs. W	1.405	1.028	1.921	2.136	0.033	
Lesiak A(2011)	M vs. W	1.411	1.074	1.853	2.475	0.013	
Glen J(2012)	M vs. W	1.332	1.048	1.694	2.343	0.019	
Nan ML(2013)	M vs. W	1.579	1.361	1.832	6.016	0.000	
Overall		1.429	1.134	1.800	3.031	0.002	

0.1   0.2   0.5   1   2   5   10
Favours Case   Favours Control

D

IL-13 (rs1800925): WM+MM VS. WW

Author	Outcome	Point	Lower limit	Upper limit	Z-Value	p-Value	Odds ratio (95% CI) with study removed
Tsunemi Y(2002)	WM+MM vs. WW	1.757	1.124	2.747	2.472	0.013	
Hummelshoj T(2003)	WM+MM vs. WW	1.568	1.030	2.388	2.095	0.036	
Chang YT(2006)	WM+MM vs. WW	1.748	1.119	2.732	2.455	0.014	
Zitnik SE(2009)	WM+MM vs. WW	1.697	0.995	2.895	1.941	0.052	
Lesiak A(2011)	WM+MM vs. WW	1.679	1.053	2.678	2.175	0.030	
Glen J(2012)	WM+MM vs. WW	1.382	1.046	1.825	2.279	0.023	
Nan ML(2013)	WM+MM vs. WW	1.893	1.297	2.764	3.306	0.001	
Overall		1.664	1.128	2.456	2.568	0.010	

0.1   0.2   0.5   1   2   5   10
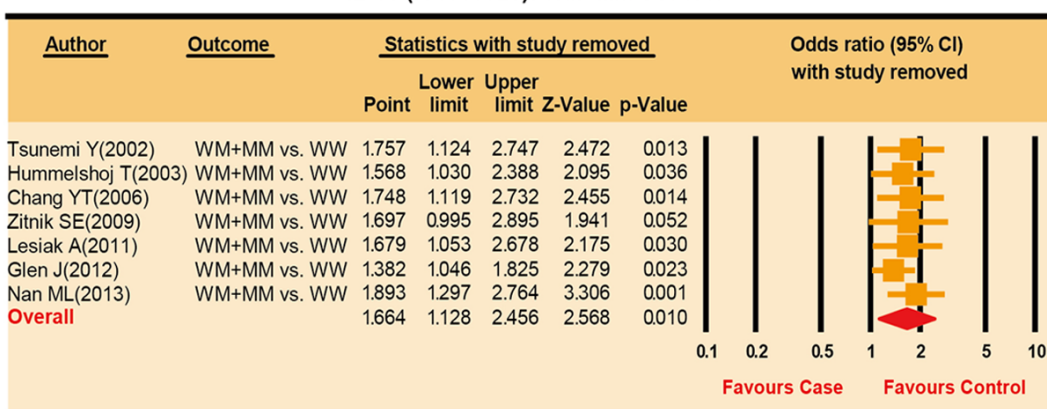Favours Case   Favours Control

Figure 6. Sensitivity analysis regarding the differences in allele gene and gene frequency of rs20541 and rs1800925 between atopic dermatitis and healthy control patients.

IL-13 gene and AD susceptibility displayed heterogeneity (allele model: I^2 = 65.109%, P = 0.009; dominant model: I^2 = 81.231%, P < 0.001). Therefore, the random effects model was utilized. The meta-analysis indicate that rs1800925 is closely associated with AD susceptibility and that genetic frequency has statistical differences between case and control groups under the allele and dominant models (allele model: OR = 1.429, 95% CI = 1.134~1.800, P = 0.002; dominant model: OR = 1.664, 95% CI = 1.128~2.456, P = 0.010) (**Figure 3C**, **3D**). The ethnicity subgroup analysis revealed that rs1800925 can predict an increased susceptibility to AD in Caucasians (allele model: OR = 1.670, 95% CI = 1.419~1.965, P < 0.001; dominant model: OR = 2.354, 95% CI = 1.393~3.976, P = 0.001). However, the association between rs1800925 and AD susceptibility is not statistically significant in Asians (allele model: OR = 1.050, 95% CI = 0.748~1.474, P = 0.779; dominant model: OR = 1.032, 95% CI = 0.744~1.431, P = 0.852) (**Figure 4C**, **4D**). The single factor meta-regression analysis results demonstrated that there is no association between publication year, sample size, ethnicity, SNPs detection method or heterogeneity (publication year: P = 0.916; sample size: P = 0.880; ethnicity: P = 0.080; detection method: P = 0.924) (**Figure 5E-H**). Furthermore, the multiple factors meta-regression analysis results found that publication year, sample size, ethnicity and detection method of SNP are not sources of heterogeneity (all P > 0.05).

Sensitivity analysis and publication bias

Sensitivity analysis confirmed that no enrolled studies exerted an obvious influence on the pooled effect size, or on the association between the SNPs in the *IL-13* gene and AD susceptibility. The symmetrical contour-enhanced funnel plots did not show any publication bias (**Figure 6**). A classic fail-safe N and Egger linear regression analysis further demonstrated that there was no publication bias (all P > 0.05) (**Figure 7**).

Discussion

We performed a detailed meta-analysis based on published data to investigate the associa-

tion between the SNPs in the *IL-13* gene and AD susceptibility. The 2 SNPs were chosen based on their prominent influence on IL-13 production and because they represent variants that up-regulate the inflammatory response. AD is a prevalent and common skin disorder which can frequently reoccur and result in a considerable cost of treatment. Therefore, it is important to investigate the risk factors of AD susceptibility [41]. The main outcome of this meta-analysis was that the SNPs of 2 loci, rs20541 and rs1800925, in the *IL-13* gene can serve as strong indicators of AD susceptibility. IL-13 is known as an immunoregulatory protein produced by activated Th2 cells and participates in the differentiation and maturation of B cells. IL-13 induces CD23 expression in B cells, enhances the expression of CD72 and MHC II antigens and can up-regulate IgE heavy chain gene transcription in B cells [42, 43]. IL-13 is produced at high levels by Th2-like cells, CD8 + cells (such as CD4 T cells, mast cells, eosinophils and basophils) and also natural killer T cells and Th-like cells. Patients diagnosed with AD have increased levels of circulating activated T cells and therefore, IL-13 is inextricably linked with the immune response state of AD [44, 45]. A single nucleotide in the coding area can result in a change in amino acids from arginine to glutamine in position 110. The 130Gln substitution accounts for the signal transducer and activator of transcription (STAT) phosphorylation in monocytes, a declined rs20541 affinity for IL-13 in the IL-13 receptor and an elevated expression of IL-13 [46]. Another SNP of *IL-13* is rs1800925. This is located in the STAT binding site within the IL-13 promoter. It may alter the binding of STAT factors and effect the expression of IL-13 in T cells [47]. AD is typically characterized by Th1/Th2 imbalance and corresponding abnormalities in immune and inflammatory cytokine secretion. Therefore, *IL-13* SNPs should have an impact on the pathogenesis of AD [48]. Taken together, our meta-analysis provides a better understanding on the role of SNPs, rs20541 and rs1800925, in regards to AD susceptibility.

A subgroup analysis was performed to understand the effect of other factors on the associa-

A. *IL-13* (rs20541): M allele VS. W allele

B. *IL-13* (rs20541): WM+MM VS. WW

C. *IL-13* (rs1800925): M allele VS. W allele
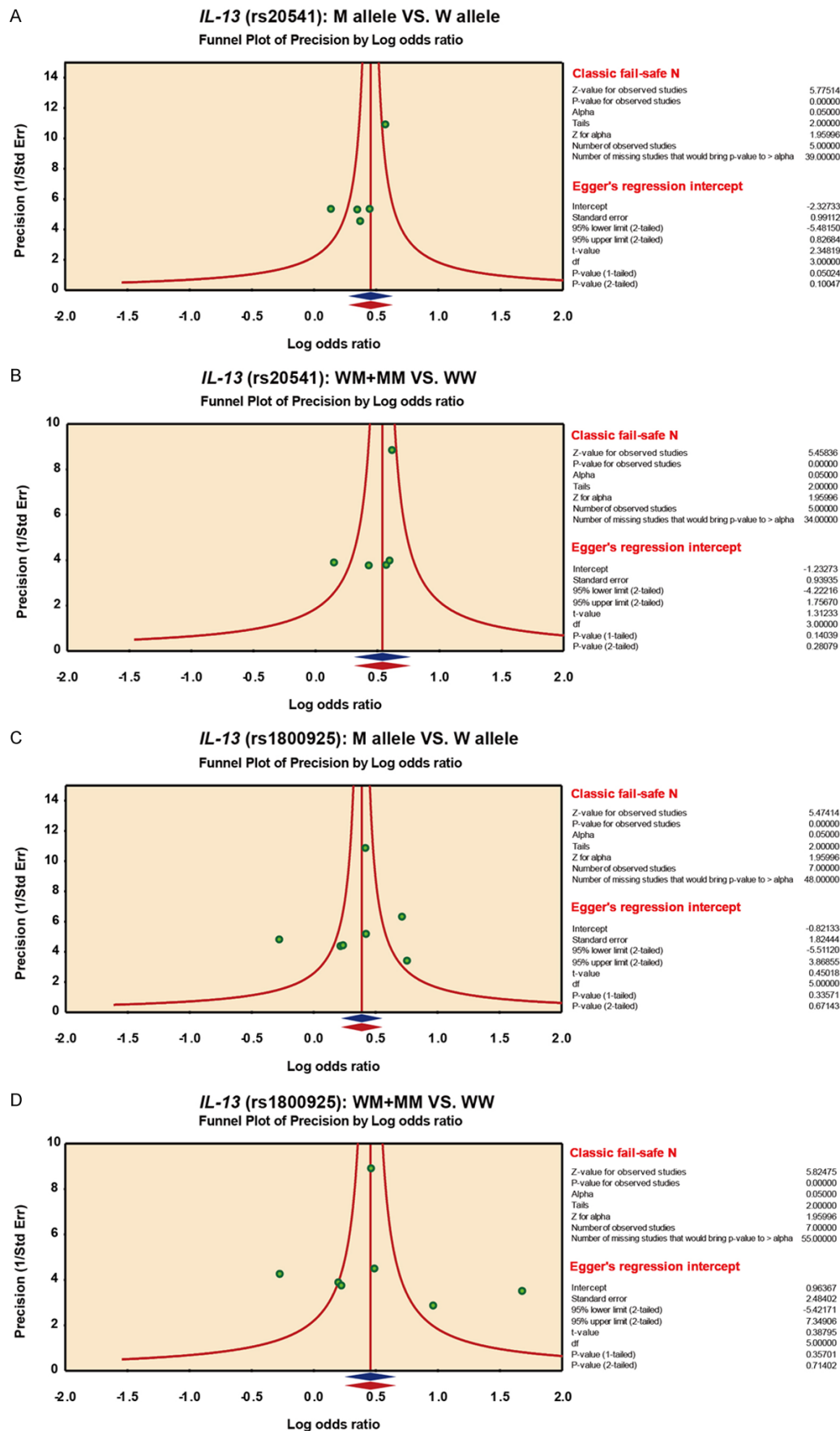
D. *IL-13* (rs1800925): WM+MM VS. WW

Figure 7. Funnel plot demonstrating publication biases regarding the differences in allele gene and gene frequency of rs20541 and rs1800925 in atopic dermatitis and healthy control patients.

tion of rs20541 and rs1800925 with AD susceptibility. From the ethnicity-stratified analysis, we conclude that rs20541 in the *IL-13* gene increases susceptibility to AD in both Asians and Caucasians. rs1800925 similarly enhances the susceptibility to AD in Asians.

We acknowledge that limitations exist in the present meta-analysis. Firstly, different methods of gene detection were used to generate the primary data used in our meta-analysis. This may contribute to a possible heterogeneity in the overall results. Secondly, the comparatively small sample size of our meta-analysis may also have a negative influence on the strength of our meta-analysis. Only 9 published studies were enrolled in our meta-analysis and this may cause a bias in the overall results. Finally, the manual search process could have led to the omission of literature which could impact the overall results.

In summary, the current meta-analysis supports the claim that SNPs, rs20541 and rs1800925, in the *IL-13* gene may be associated with AD susceptibility. A particularly interesting finding was that an ethnicity difference exists in the association between rs20541 and AD susceptibility. Further studies with larger data sets and higher quality data are required to confirm these results.

Disclosure of conflict of interest

None.

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