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Original Article

Association of rs2228570 polymorphism of vitamin D receptor gene with degenerative disc disease: a meta-analysis involving 2947 subjects

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Abstract: This study aimed to explore the association between the rs2228570 polymorphism in the vitamin D receptor gene and degenerative disc disease (IDD), especially in European. We perform a meta-analysis to analyze the association after searching the relevant studies through China National Knowledge Infrastructure (CNKI), PubMed, Medline and EMBASE databases. And odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of the association. A total of 10 studies involving 1,465 cases and 1,482 controls were included in the meta-analysis. Overall, there was not significant risk between rs2228570 polymorphism and degenerative disc disease in any genetic models. In addition, stratified analyses by ethnicity revealed similar results. However, stratified analyses by others indicates an association between IDD and the FF genotype (OR=0.62, 95% CI=0.43-0.90, P=0.486) in age =40, and the F allele (OR=0.84, 95% CI=0.73-0.96, *P*=0.992), FF genotype (OR=0.78, 95% CI=0.65-0.93, *P*=0.853) in sample size > 300, and ff genotype (OR=0.91, 95% CI=1.11-3.29, *P*=0.783), FF genotype (OR=0.70, 95% CI=0.51-0.96, *P*=0.258) in Northern European. This meta-analysis suggested that the rs2228570 polymorphism may not be associated with degenerative disc disease. However, there existed some diversities, especially in age < 40, sample size > 300, countries in Northern Europe, suggesting that carrying the VDR FokI F allele may be a protective factor against IDD development. But a large number of well-designed studies are still required to assess this polymorphism and degenerative disc disease.

Keywords: rs2228570 polymorphism, vitamin D receptor gene, degenerative disc disease, meta-analysis

Introduction

Intervertebral disc disease (IDD), characterized by intervertebral disc herniation and/or sciatic pain, is a common musculoskeletal problem in the world [1]. In recent decades, low-back pain (LBP) mainly caused by lumbar disc disease have affected more than 50% of population during a lifetime [2]. LBP can not only lead to reduced physical activity, decreased quality of life, and psychological distress, but also bring enormous economic pressures on society [3, 4]. It has been one of the most prominent problems in the industrialized countries.

Although the explicit pathogenic mechanisms leading to intervertebral disc disease are still unclear, it is generally believed that age and environmental factors such as sporting activities, occupation, injury, and smoking contribute to its development [5-7]. Beyond that, the outcome of many studies over the past decades has shown that numerous genes plays a critical role in IDD, for example, Collagen I [8], Collagen IX [9], Aggrecan [10], COL9A2 [11], Interleukins [12] and vitamin D receptor.

The vitamin D receptor gene (VDR) was studied as a genetic factor predisposing to spine pathologies since 1998 and plays a part in normal bone mineralization and remodeling [13, 14]. It is an endocrine member belongs to the nuclear receptor superfamily for steroid hormones [15]. Its gene polymorphisms are thought to contribute to osteoarthritis, osteoporosis and degenerative disc disease [16]. Up to date, several locations have been used to assess the association of VDR and degenerative disc disease in

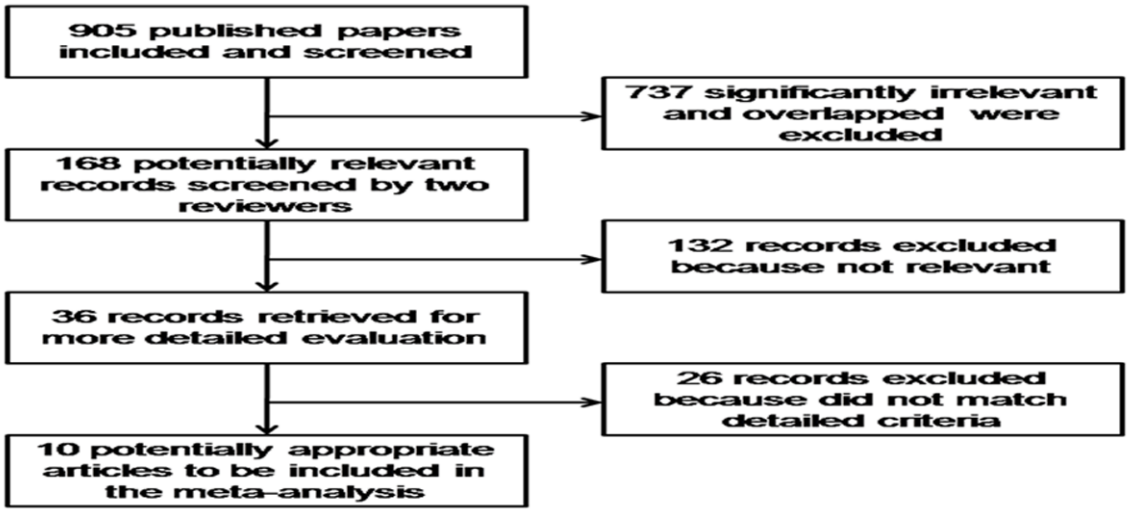

Figure 1. Study flow diagram of search strategy.

Table 1. The characteristics of the selected studies

First author	Year	Country	Ethnicity	Sample Size (Case/Control)	Genotype Distribution (Case/Control)			P for HWE
					T/T	T/t	t/t	
Noponen-Hietala	2003	Filand	Caucasian	100/100	11/25	12/26	6/5	0.630
Chen	2007	China	Asian	81/101	18/36	51/48	12/17	0.883
Eser	2010	Turkey	Caucasian	150/150	81/67	52/67	17/16	0.901
Eskola	2010	Denmark	Caucasian	66/154	29/45	26/91	11/18	0.010
Kelempisioti	2011	Finland	Caucasian	150/246	81/111	57/119	12/16	0.031
Cauci	2012	Italy	Caucasian	234/70	105/25	105/36	24/9	0.476
Vieira	2014	Brazil	Caucasian	121/131	54/75	50/46	17/10	0.434
Colombini	2014	Italy	Caucasian	267/220	117/89	120/99	30/32	0.601
Serrano	2014	Mexico	Caucasian	100/100	20/32	65/51	15/17	0.664
Colombini	2015	Italy	Caucasian	267/254	117/101	120/117	30/36	0.821

HWE, Hardy-Weinberg equilibrium.

different populations. Among these polymorphisms, The C > T single nucleotide polymorphism rs2228570 in the VDR is reported that may could affect the intervertebral disc disease. However, the results were often inconsistent and ambiguous. To our knowledge, there was only one meta-analysis once studied this location three years ago [17]. But it had some limitations: First, they only included 5 papers. From one of them, the author did not get sufficient data, and the original data of two other they included were inaccurate (the data from them are not identical to the original articles); Second, in their article, they admitted that as limited studies were included for the association investigation, they did not perform subgroup analysis.

Considering the reasons above, we decided to add the latest data and made subgroup analysis with the aim of providing a clearer and correct understanding of the relationship between the rs2228570 polymorphism and degenerative disc disease.

Materials and methods

Search strategies

We sought to search the relevant epidemiologic studies that investigated the association of

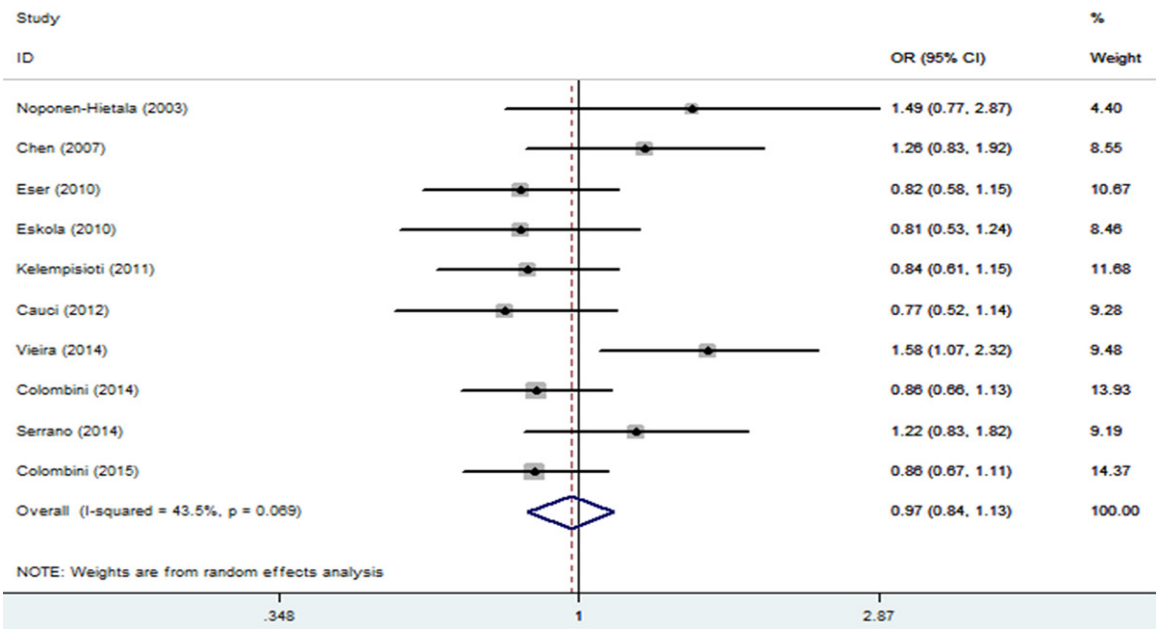

Figure 2. Forest plot for the meta-analysis of the association between rs2228570 polymorphism and degenerative disc disease (under allele comparison model).

rs2228570 polymorphism with degenerative disc disease. China National Knowledge Infrastructure (CNKI), PubMed, Medline and EMBASE databases were retrieved by two authors independently to identify available articles published up to March 2015. The following terms were utilized: "disc", "lumbar", "degeneration", "vitamin D receptor gene", "polymorphism, variation, variant, mutation" "genetic*", "rs2228570". These words were combined to be consecutively entered, including all alternative locations and combinations. We also screened the reference lists of all cited articles and relevant reviews to confirm other potentially valuable studies.

Inclusion and exclusion criteria

For the meta-analysis, studies were included if they met the following criteria: (1) case-control studies that had original data to assess quantitatively the relationship of rs2228570 polymorphism and degenerative disc disease; (2) cases and controls were eligible regardless of country, ethnicity and age; (3) providing sufficient data for calculation of odds ratio (OR) and 95% confidence interval (CI).

While for the exclusion criteria, we provided as follows: (1) not for rs2228570 polymorphism research; (2) studies containing overlapping data; (3) articles but not case-control study; (4) studies that investigated rs2228570 variants as makers for response to therapy; (6) studies in which the number of genotypes or alleles were not offered.

Data extraction

Two authors strictly extracted relevant information from all retrieved publications according to the inclusion criteria. Discrepancy was settled by two authors or a third author. The following data were collected from each study: first author's surname, year of publication, original country, and ethnicity, the number of cases and controls and genotype frequency information. We will verify the accuracy of information by comparing data extracted by two authors. If more than one study includes the same population, we only included the most valuable study in this meta-analysis.

Statistical analysis

We used the data from studies investigating the association between rs2228570 polymorphism and IDD to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) to evaluate the strength of the association. The statistical significance of the pooled OR was evaluated by the Z test. Hardy-Weinberg equi-

Table 2. Overall and subgroup meta-analysis of the association between rs2228570 polymorphism and degenerative disc disease under genetic models

Groups	N	Allelic		Homozygout		Heterozygous		Dominant		Recessive	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Total	10	0.9 (0.84, 1.13)	0.069	0.98 (0.77, 1.25)	0.288	1.02 (0.81, 1.30)	0.296	0.99 (0.79, 1.24)	0.433	0.96 (0.74, 1.24)	0.005
Asian	1	1.2 (0.83, 1.92)	NA	0.41(0.56, 3.58)	NA	0.66 (0.29, 1.30)	NA	0.86 (0.38, 1.92)	NA	1.94 (1.00, 3.76)	NA
Caucasian	10	0.95 (0.81, 1.11)	0.081	0.95 (0.74, 1.23)	0.253	1.07 (0.83, 1.37)	0.297	1.00 (0.79, 1.27)	0.349	0.90 (0.70, 1.15)	0.019
European	8	0.88 (0.78, 1.00)	0.534	0.87 (0.67, 1.14)	0.204	1.03 (0.79, 1.34)	0.268	0.94 (0.73, 1.21)	0.531	0.81 (0.69, 0.96)	0.130
Eastern	2	0.97 (0.75, 1.26)	0.130	1.41 (0.58, 3.44)	0.045	0.98 (0.57, 1.69)	0.225	0.97 (0.57, 1.63)	0.685	0.97 (0.67, 1.39)	0.012
Northern	3	0.89 (0.70, 1.13)	0.260	1.03 (0.46, 2.29)	0.584	1.91 (1.11, 3.29)	0.783	1.52 (0.91, 2.54)	0.615	0.70 (0.51, 0.96)	0.258
Southern	3	0.84 (0.72, 1.00)	0.888	0.72 (0.41, 1.25)	0.981	0.81 (0.57, 1.16)	0.950	0.76 (0.54, 1.06)	0.995	0.82 (0.66, 1.04)	0.756
Age											
> 40	4	0.94 (0.80, 1.12)	0.185	0.98 (0.67, 1.45)	0.271	1.04 (0.63, 1.72)	0.212	0.96 (0.67, 1.38)	0.301	1.01 (0.67, 1.53)	0.061
< 40	2	0.82 (0.62, 1.07)	0.955	0.91 (0.51, 1.61)	0.898	1.67 (0.94, 2.97)	0.451	1.24 (0.72, 2.14)	0.535	0.62 (0.43, 0.90)	0.486
Sample											
> 300	5	0.84 (0.73, 0.96)	0.992	0.77 (0.57, 1.04)	0.920	0.96 (0.71, 1.30)	0.536	0.86 (0.64, 1.14)	0.777	0.78 (0.65, 0.93)	0.853
< 300	5	1.23 (0.97, 155)	0.227	1.55 (1.02, 2.36)	0.585	1.15 (0.77, 1.70)	0.133	1.28 (0.88, 1.87)	0.346	1.33 (0.80, 2.21)	0.015

N: total number of studies involved in the analysis; NA: the data were not available.

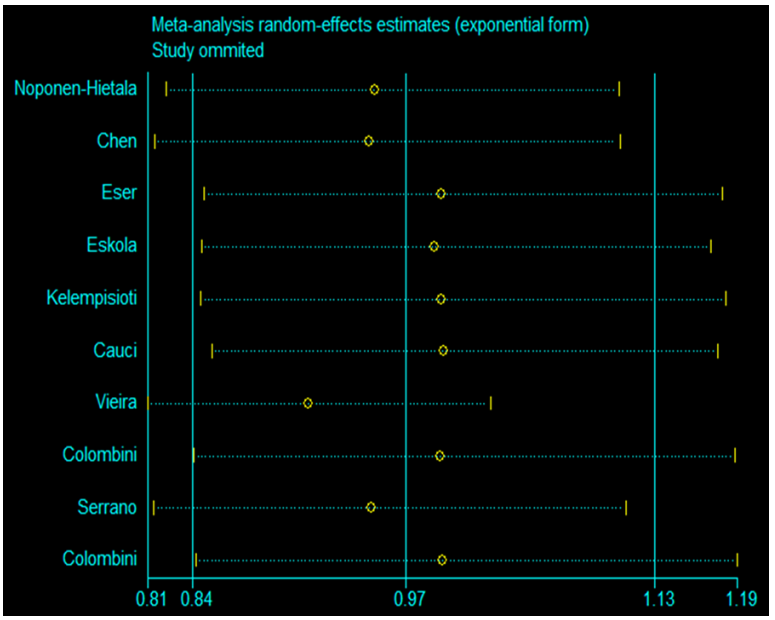

Figure 3. One-way sensitivity analysis of the pooled ORs and 95% CI for the overall analysis, omitting each dataset in the meta- analysis.

librium (HWE) in the control group for each study was determined by Chi square test; $P < 0.05$ was considered significant. We calculated the pooled ORs for allele comparison model (F vs. f), homozygote model (FF vs. ff), heterozygote model (Ff vs. ff), dominant model [(Ff+FF) vs. ff] and recessive model [FF vs. (ff+Ff)], respectively. Heterogeneity was evaluated with the chi-square-based Q test and it was considered significantly when P was below 0.01. In addition, heterogeneity was also assessed by the I^2 statistic (I^2=0-25%: no heterogeneity; I^2=25-50%: moderate heterogeneity; I^2=50-75%: large heterogeneity; I^2=75-100%: extreme heterogeneity [18]. When the heterogeneity was obvious, the random-effect model was used to calculate the pooled OR [19], otherwise the fix-effect model was used [20]. Moreover, we also performed the stratified analysis by ethnicity, age, sample size and regions of Europe to explore the source of the heterogeneity. In order to assess the stability of the results, we performed sensitivity analysis and utilized funnel plots to estimate the potential publication bias. Begg's [21] and Egger's [22] tests were also used to evaluate the publication bias ($P < 0.05$ indicates a significant publication bias). All analyses for this meta-analysis were performed with STATA version 12.0 (Stata Corporation, College Station, TX).

Results

Characteristics of included studies

The flow diagram of the selection process of this literature was given in **Figure 1**. Eventually, a total of 10 eligible studies met the inclusion criteria including 1,465 cases and 1,482 controls [12, 23-31]. Of the 10 papers of polymorphisms, there were 9 studies performed in Caucasians, 1 study in Asian. The characteristics of the selected studies in the current meta-analysis are summarized in **Table 1**.

Quantitative synthesis

We conducted this meta-analysis on the association between rs2228570 polymorphism with degenerative disc disease. Overall, no evidence of significant risk between rs2228570 polymorphism and degenerative disc disease was found in any genetic models (allelic model: OR=0.97, 95% CI=0.84-1.13, P=0.069 (**Figure 2**); homozygote model: OR=0.98, 95% CI=0.77-1.25, P=0.288; heterozygote model: OR=1.02, 95% CI=0.81-1.30, P=0.296; dominant model: OR=0.99, 95% CI=0.79-1.24, P=0.433; recessive model: OR=0.96, 95% CI =0.74-1.24, P=0.005). In addition, **Table 2** showed the results of the overall analysis and the subgroup analysis.

Moderate heterogeneity was found in allelic genetic model and large heterogeneity in recessive genetic model of our current meta-analysis. Subgroup analysis stratified by ethnicity, age, sample size and regions of Europe, revealed that no associations existed in Caucasians or Asians, in subjects with age < 40 or > 40, in sample size and in different regions of Europe (**Table 2**).

Sensitivity analysis and publication bias

In order to evaluate the stability of the pooled results, we further conducted sensitivity analysis by sequential omission of individual studies (**Figure 3**). In the sensitivity analysis of IDD risk,

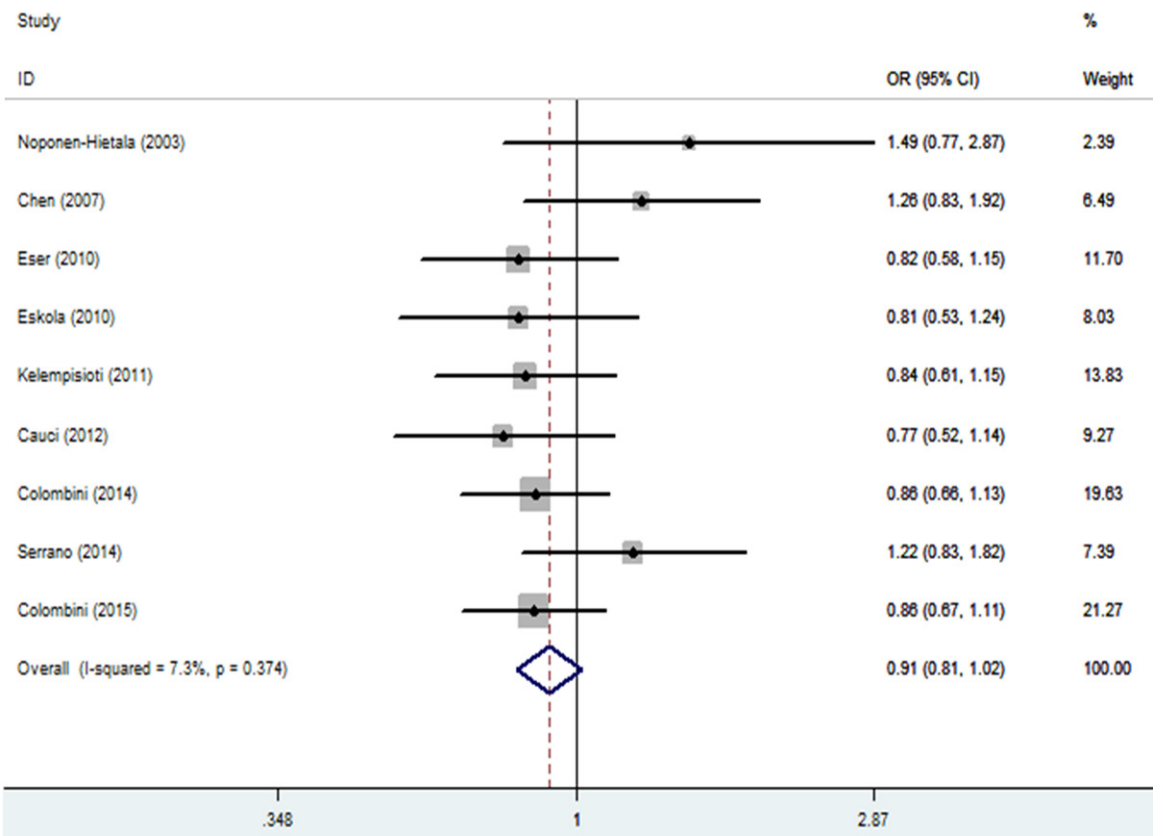

Figure 4. Allele comparison model after one study deleted.

only one study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs, no other study impact on the pooled OR qualitatively (**Figure 4**). And though excluding two papers which were not consistent with Hardy-Weinberg equilibrium, the result was still stable.

Both Begg's and Egger's test were performed to assess the publication bias of the literatures for the association between rs2228570 polymorphism and degenerative disc disease. The shape of funnel plots did not showed obvious asymmetry. Our statistical data also did not show an evidence of publication bias (Egger's test P=0.109; Begg's test P=0.283) (**Figures 5**, **6**).

Discussion

Low back pain (LBP) is a common musculoskeletal problem causing disability and it is the primary cause of activity limitation and work absence throughout the world [32]. IDD is considered to be the leading cause of LBP. Many environmental and other risk factors probably contribute to the acceleration of spinal degeneration. Information gained from studies suggests that genetic factors are playing crucial roles in the onset and progression of intervertebral disc degeneration (IDD) [33, 34]. There are a lot of genes that have been explored to investigate the associated with IDD. Vitamin D receptor gene which is located on chromosome 12 (12q12-q14) is the first gene reported potentially related to IDD risks [14, 35].

However, as an important location of the VDR gene, only one meta-analysis focused on rs2228570 mutation in IDD 3 years ago. But it had some limitations: First, they only included 5 papers. From one of them, the author did not get sufficient data, and the original data of two other they included were inaccurate (the data from them are not identical to the original articles); Second, in their article, they admitted that as limited studies were included for the association investigation, they did not perform subgroup analysis.

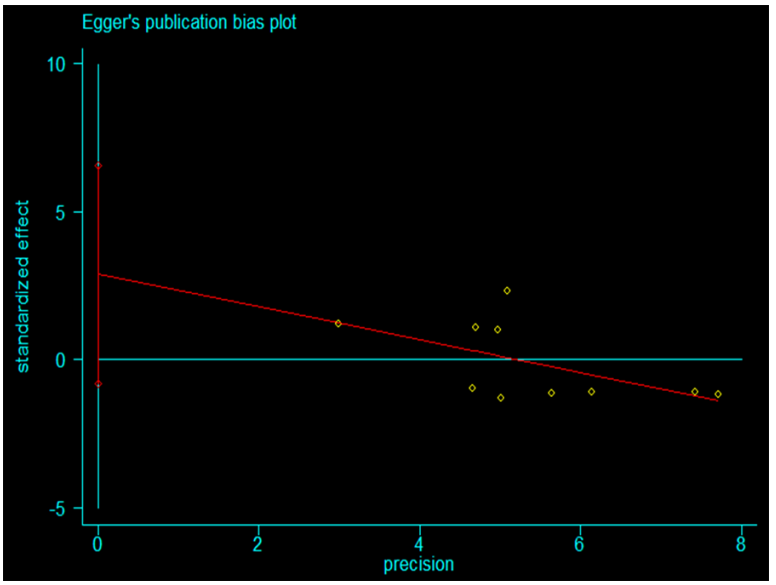

Figure 5. Egger's test was held to detect potential publication bias.

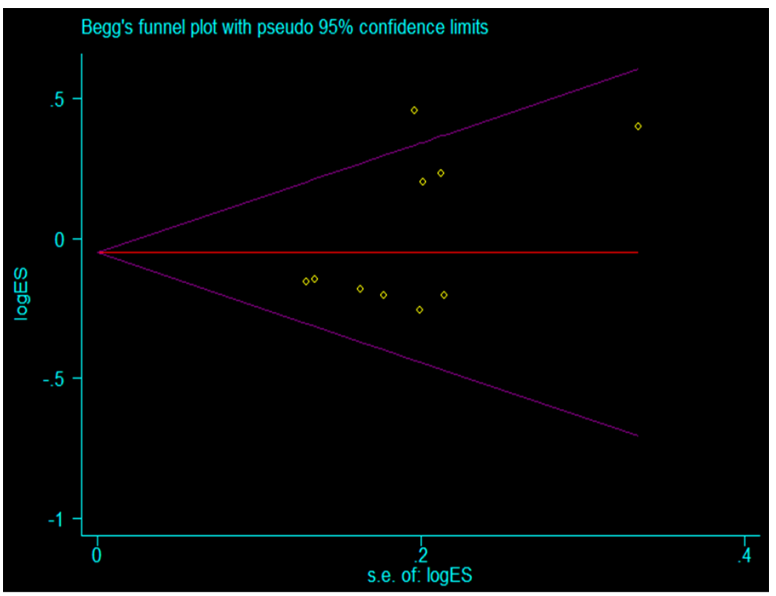

Figure 6. Begg's test was held to detect potential publication bias.

Therefore, to settle an argument, we performed the most comprehensive review on the association between rs2228570 polymorphism with degenerative disc disease so far. This present meta-analysis included 1,465 cases and 1,482 controls from 10 case-control studies and is the largest scale meta-analysis up to now.

On the whole, our results suggested that the rs2228570 polymorphism may not be associated with degenerative disc disease. In addition, stratified analyses by ethnicity revealed similar results. However, stratified analyses by others indicates an association between IDD and the FF genotype in age < 40, and the F allele, FF genotype in sample size > 300, and ff genotype, FF genotype in Northern European. These results revealed that there may existed some diversities including age < 40, sample size > 300, countries in Northern Europe and carrying the VDR FokI F allele may be a protective factor against IDD development. In these articles, two of them were not consistent with Hardy-Weinberg equilibrium and they were all from Northern Europe. Although after excluding them the net result remained stable, there was only one paper left from Northern European. Thus we may get a bit of a lopsided result.

Although meta-analyses have been made to resolve the matter, we must admit that some limitations should be taken into account when interpreting our research. First, the sample size of the published studies was not enough to confirm an adequate large-scale research on the relationship between rs2228570 polymorphism and degenerative disc disease. Second, most data of included papers were from Caucasian population. There was only one from Asian and none from other population like Africans so that we cannot make some relative precise conclusions and this may increase the risk of false-negative findings in all population levels. Third, some studies were excluded from our research because of not providing the original data, which may result in selection bias. Fourth, our result was based on unadjusted estimates, while a more precise analysis should be conducted adjusted by other

factors like age, BMI, height, weight and so on. In addition, papers included in our articles only were written in English and Chinese, and therefore some qualified studies written in other languages were not included. Therefore, we are not sure whether there is a significant association between rs2228570 polymorphism and degenerative disc disease in the whole population.

In conclusion, the results of our meta-analysis indicate that the rs2228570 polymorphism may not be associated with degenerative disc disease. However, there existed some diversity in age, sample size and region. Hence, we cannot predict the risk of IDD just by the single gene but to synthesize all kinds of factors including environment, ethnicity, region and different genes. A large number of well-designed studies should be conducted to re-evaluate the relationship.

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Disclosure of conflict of interest

None.

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