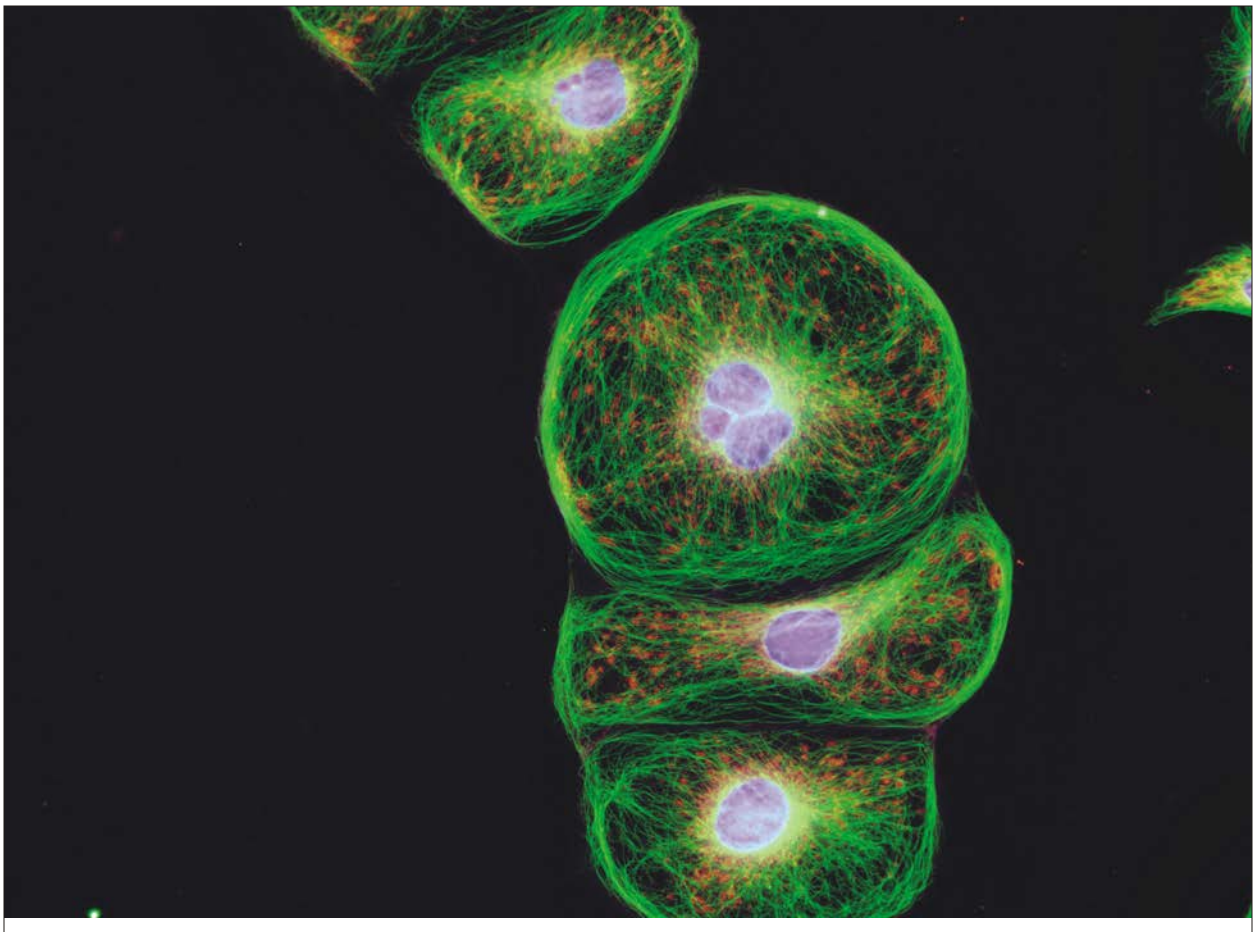

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Association of IL-10 (−1082 G/A Polymorphism) with Multiple Sclerosis Risk: A Systematic Review and Meta-Analysis

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ABSTRACT

Multiple Sclerosis (MS) is a chronic demyelinating disease of the Central Nervous System (CNS) that manifests with inflammation and axonal degeneration. We decided to perform a meta-analysis to pool all available results of the association between IL-10 (−1082G/A) polymorphism and MS risk. This is a genetic meta-analysis conducted with respect to the association between the IL-10 polymorphism and MS risk. We accomplished a search in PubMed and Scopus databases to identify articles published up to Jun 2013 that examined the associations between IL-10 (1082 G/A) polymorphism and MS. Odds Ratios (OR) with the 95% Confidence Intervals (CI) were used to assess the association. A total of eight case-control studies, including 1517 cases and 1059 controls were selected. All the proposed models were associated with a non-significant increased risk of MS. The A allele carriers (homo and heterozygotes) had a 50% non-significant increased risk of MS, when compared with the homozygote G (OR = 1.50, 95% CI = 0.91-2.48, p = 0.111). In the subgroup analysis by ethnicity, non-significant increased MS risks were found among Europeans for all genetic models and the A allele carriers (homo and heterozygotes) had a 59% non-significant increased risk of MS (OR = 1.59, 95% CI = 0.91-2.79, p = 0.104). For Asian ethnicity (Iran), also no significant association between this polymorphism and MS risk was observed in all comparison models. This meta-analysis provided evidence that IL-10 (−1082 G/A) polymorphism is associated with an increased risk of MS, especially in Europeans. Current knowledge is not sufficient to explain the role of the aforementioned polymorphisms in MS pathogenesis.

Key words: Multiple sclerosis, IL-10 (interleukin-10), meta-analysis, polymorphism, risk

INTRODUCTION

Multiple Sclerosis (MS) is a chronic demyelinating disease of the Central Nervous System (CNS) that manifests with inflammation and axonal degeneration (Zhang *et al*., 2011). Its major characteristics include numbness, paresis, visual disturbance, bladder dysfunction and others (Weissert, 2013). Although the precise cause of MS is currently unknown, both genetic and environmental factors have been shown to contribute to the pathogenesis of MS, so this is a multifactorial disease (Gourraud *et al*., 2012). Twin studies have indicated that genetic factors have an important role in susceptibility to Multiple Sclerosis (Hawkes and Macgregor, 2009). Dysregulation of inflammatory and anti-inflammatory cytokines production has been shown in

experimental models of Experimental Autoimmune Encephalomyelitis (EAE) and patients with MS (Izad *et al*., 2010). Interleukin-10 (IL-10) is an anti-inflammatory cytokine that down-regulates the immune response by reducing T cell function and MHC class II expression in APCs (Rai and Wakeland, 2011). Moreover, it has been shown that over expression of IL-10 takes place during remission phases in MS patients (Mihailova *et al*., 2005). Interleukin-10 gene knockout in animal model makes more severe and inducing of IL-10 expression in the CNS inhibits EAE (Myhr *et al*., 2002). There are three important polymorphisms in the promoter region of IL-10 gene including -1082 (G/A), -819 (T/C) and -592 (A/C) (Wergeland *et al*., 2005). These polymorphisms may affect the expression of this cytokine (8). Several studies have investigated association between -1082 G/A (rs 1800896) polymorphism in IL-10 gene and susceptibility to MS (Azarpira *et al*., 2010; Forte *et al*., 2006; Luomala *et al*., 2003; Doncel *et al*., 2002; Maurer *et al*., 2000; Mihailova *et al*., 2005; Mirowska-Guzel *et al*., 2011; Myhr *et al*., 2002; Pickard *et al*., 1999; Rai and Wakeland, 2011) but until now, there is no conclusive result. In order to derive a more precise conclusion, we decided to perform a meta-analysis to pool all available results of the association between IL-10 (–1082 G/A) polymorphism and MS risk. This is a genetic meta-analysis conducted with respect to the association between the IL-10 polymorphism and MS risk.

MATERIAL AND METHODS

Publication search: We accomplished a search in PubMed and Scopus databases to identify articles published up to Jun 2013 that examined the associations between IL-10 (1082 G/A) polymorphism and MS. Combination of fallowing key words were used: Interleukin -10 OR IL-10, genetic polymorphisms and multiple sclerosis and all possible combinations. We investigated potentially relevant publications by examining their titles and abstracts. All studies matching the eligible criteria were selected. No language restriction was applied.

Inclusion criteria: Studies that observed the IL-10 (–1082G/A) polymorphism and MS susceptibility, have a case-control study design, have genotype distributions in both cases and controls for estimating an Odds Ratio (OR) with 95% Confidence Interval (CI), were included.

Exclusion criteria: Publications that have repeating data, familial studies and review articles were excluded.

Data extraction: Data was extracted by two reviewers (FR and HG) individually according to the mentioned inclusion criteria. Each reviewer extracted following information independently: First author, year of publication, country, ethnicity, number of cases and controls, genotyping method and genotype distribution in cases and controls.

Statistical analysis: We used ORs with 95% CI to evaluate the strength of the association between the IL-10 –1082G/A polymorphism and susceptibility to MS. The pooled ORs were computed for dominant model (AA+AG vs. GG), recessive model (AA vs. AG+GG), heterozygote comparison (AG vs. GG) and homozygote comparison (AA vs. GG). The pooled ORs were calculated by a fixed-effects model (the Mantel- Haenszel method) or a random-effects model (the Dersimonian and Laird method) according to the heterogeneity. Heterogeneity was evaluated by a chai2-based Q statistic and was considered statistical significant at p-value less than 0.10. When the p-value is greater than 0.10, the pooled OR estimate of each study was calculated by the fixed-effects model,

otherwise, a random-effect model was used. Publication bias was analyzed by several methods. Visual inspection of asymmetry in funnel plots was carried out. The Begg's test and Egger's test were also used to statistically assess publication bias. Sensitivity analysis was also achieved by sequence excluding individual study to check the stability of the result. All statistical tests were carried out by using STATA 11.0.

RESULTS

Study characteristics: A comprehensive search in Scopus and PubMed databases was carried out. Overall, 54 studies were identified as potentially relevant to our searching strategy. After screening titles and abstracts, eight records excluded due to repeating and 36 records excluded because of irrelevance. Hence, 10 articles were selected for full-text review and data extraction. Two studies were excluded because they did not contain genotype data for the CTLA-4 polymorphism (Izad *et al*., 2010; Doncel *et al*., 2002), so, a total of eight case-control articles remain due to our inclusion criteria (Azarpira *et al*., 2010; Izad *et al*., 2010; Luomala *et al*., 2003; Maurer *et al*., 2000; Mihailova *et al*., 2005; Mirowska-Guzel *et al*., 2011; Myhr *et al*., 2002; Pickard *et al*., 1999). Study flow-chart is shown in Fig. 1. Thus, the meta-analysis carried out with a total of 1517 cases and 1059 controls of 8 separate comparisons. A summary of selected studies is shown in Table 1. Table 1 also contains genotype frequencies in cases and controls.

Meta-analysis results: The primary results of meta-analysis are shown in Fig. 2: (a) Dominant model (AA+AG vs. GG), (b) Recessive model (AA vs. AG+GG), (c) Homozygote comparison (AA vs. GG) and (d) Heterozygote comparison (AG vs. GG) and a summary of results is in Table 2. All the proposed models were associated with a non-significant increased risk of MS (Table 2). The A allele carriers (homo and heterozygotes) had a 50% non-significant increased risk of MS, when

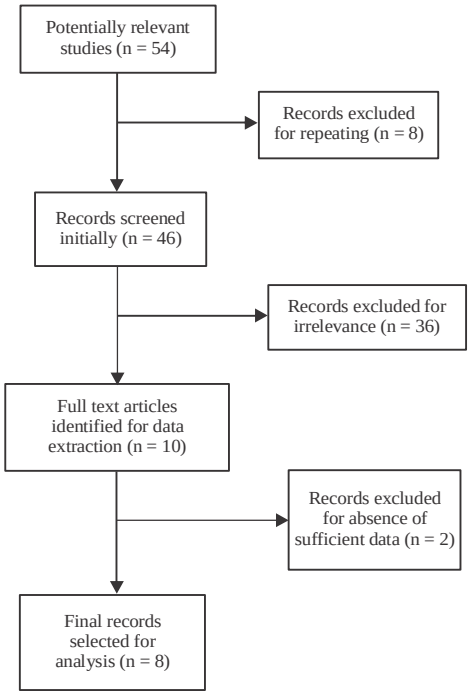

Fig. 1: Study flow chart

compared with the homozygote G (OR = 1.50, 95% CI = 0.91-2.48, p = 0.111). In the subgroup analysis by ethnicity, non-significant increased MS risks were found among Europeans for all genetic models and the A allele carriers (homo and heterozygotes) had a 59% non-significant

Table 1: Characteristics of case-control studies included in meta-analysis

				Multiple sclerosis disease			Controls		
First author	Country	Ethnicity	Genotyping method	GG	GA	AA	GG	GA	AA
Mirowska-Guzel *et al*. (2011)	Poland	European	PCR-RFLP	45	123	56	44	99	50
Azarpira *et al*. (2010)	Iran	Asian	ARMS PCR	6	83	21	5	79	16
Forte *et al*. (2006)	Italy	European	ARMS-PCR	18	44	29	52	101	67
Mihailova *et al*. (2005)	Bulgaria	European	PCR-SSP	9	27	19	9	36	41
Luomala *et al*. (2003)	Finland	European	Direct sequencing	21	62	33	88	177	135
Myhr *et al*. (2002)	Norway	European	Sequencing	48	72	48	21	43	23
Maurer *et al*. (2000)	Germany	European	AD-PCR	38	92	51	19	37	29
Pickard *et al*. (1999)	UK	European	PCR	56	94	39	63	90	58

Table 2: Meta-analysis for the association between Multiple sclerosis risk and the IL-10 –1082G/A polymorphism

			Heterogeneity test		Hypothesis test			Egger test		Begg test		
Populations	Model	No. of studies	Q	p	Z	p	I^2 (%)	t	p	Z	p	Pooled OR (95% CI)
Overall												
Dominant	R	8	110.41	0.000	1.59	0.111	93.7	0.65	0.540	2.10	0.035	1.50 (0.91-2.48)
Recessive	R	8	119.23	0.000	0.51	0.610	94.1	0.68	0.523	1.61	0.108	1.21 (0.58-2.22)
Heterozygote	R	8	95.09	0.000	0.54	0.590	92.6	0.14	0.891	0.12	1.000	1.18 (0.64- 2.17)
Homozygote	R	8	212.37	0.000	0.35	0.727	96.7	0.31	0.766	0.87	0.386	1.20 (0.43- 3.38)
Caucasian												
Dominant	R	7	106.58	0.000	1.62	0.104	94.4	0.74	0.492	1.80	0.072	1.59(0.91-2.79)
Recessive	R	7	119.13	0.000	0.46	0.642	95	1.00	0.365	1.50	0.133	1.21 (0.58-2.22)
Heterozygote	R	7	95.05	0.000	0.46	0.643	93.7	0.27	0.800	0.30	0.764	1.17 (0.60-2.30)
Homozygote	R	7	211.97	0.000	0.28	0.780	97.2	0.55	0.603	0.90	0.368	1.18 (0.37-3.74)
Asian (Iran)*												
Dominant	F	1	-	-	0.02	0.981	-	-	-	-	-	1.00 (0.68-1.47)
Recessive	F	1	-	-	0.49	0.623	-	-	-	-	-	1.19 (0.59-2.41)
Heterozygote	F	1	-	-	0.66	0.511	-	-	-	-	-	1.24 (0.65 -2.37)
Homozygote	F	1	-	-	0.90	0.366	-	-	-	-	-	1.39 (0.68 -2.84)

*The other ethnicity was only a single study

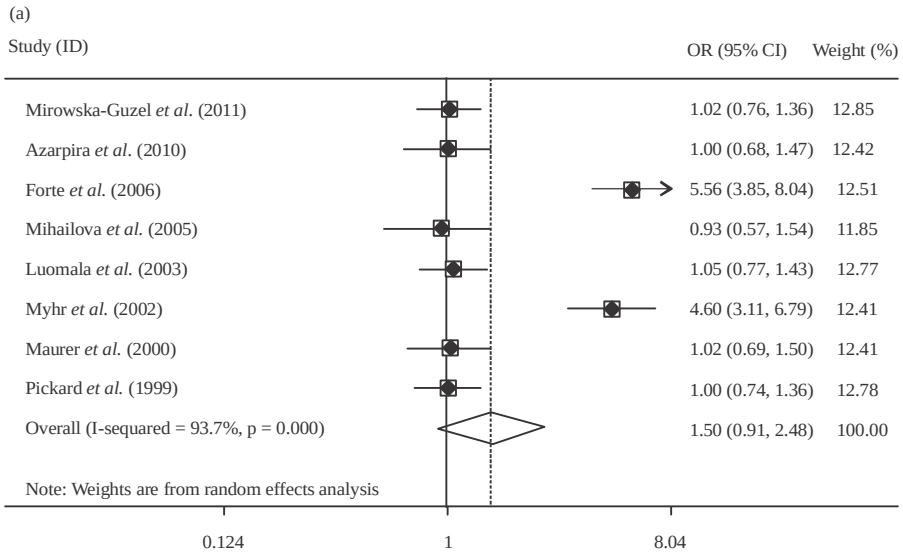

Fig. 2(a-d): Continue

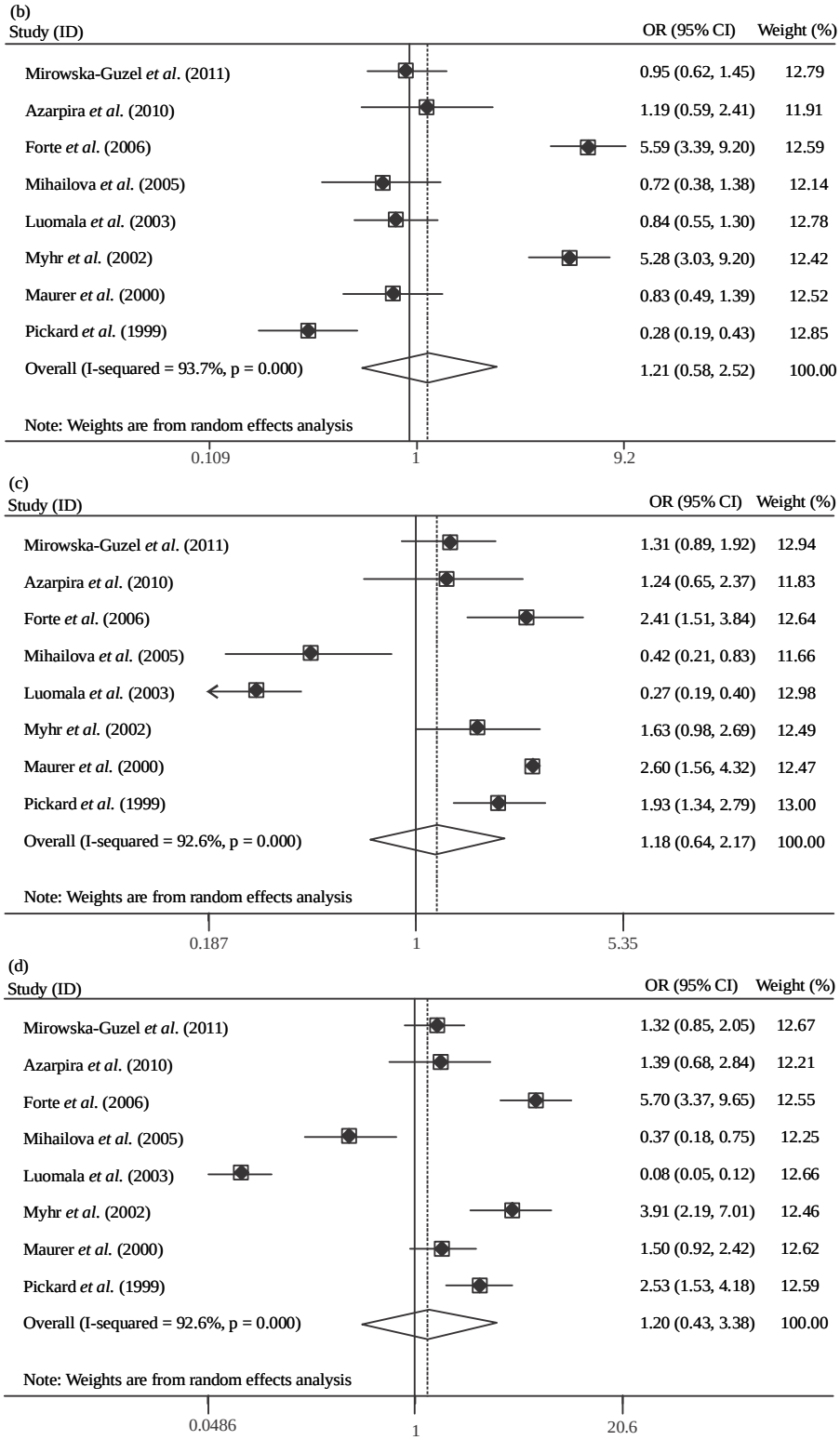

Fig. 2(a-d): Meta-analysis for the association between MS risk and the IL-10 -1082 G/A polymorphism, (a) Dominant model, (b) Recessive model, (c) Heterozygote comparison and (d) Homozygote comparison

increased risk of MS (OR = 1.59, 95% CI = 0.91-2.79, p = 0.104) (Fig. 3). For Asian ethnicity (Iran), also no significant association between this polymorphism and MS risk was observed in all comparison models (Table 2).

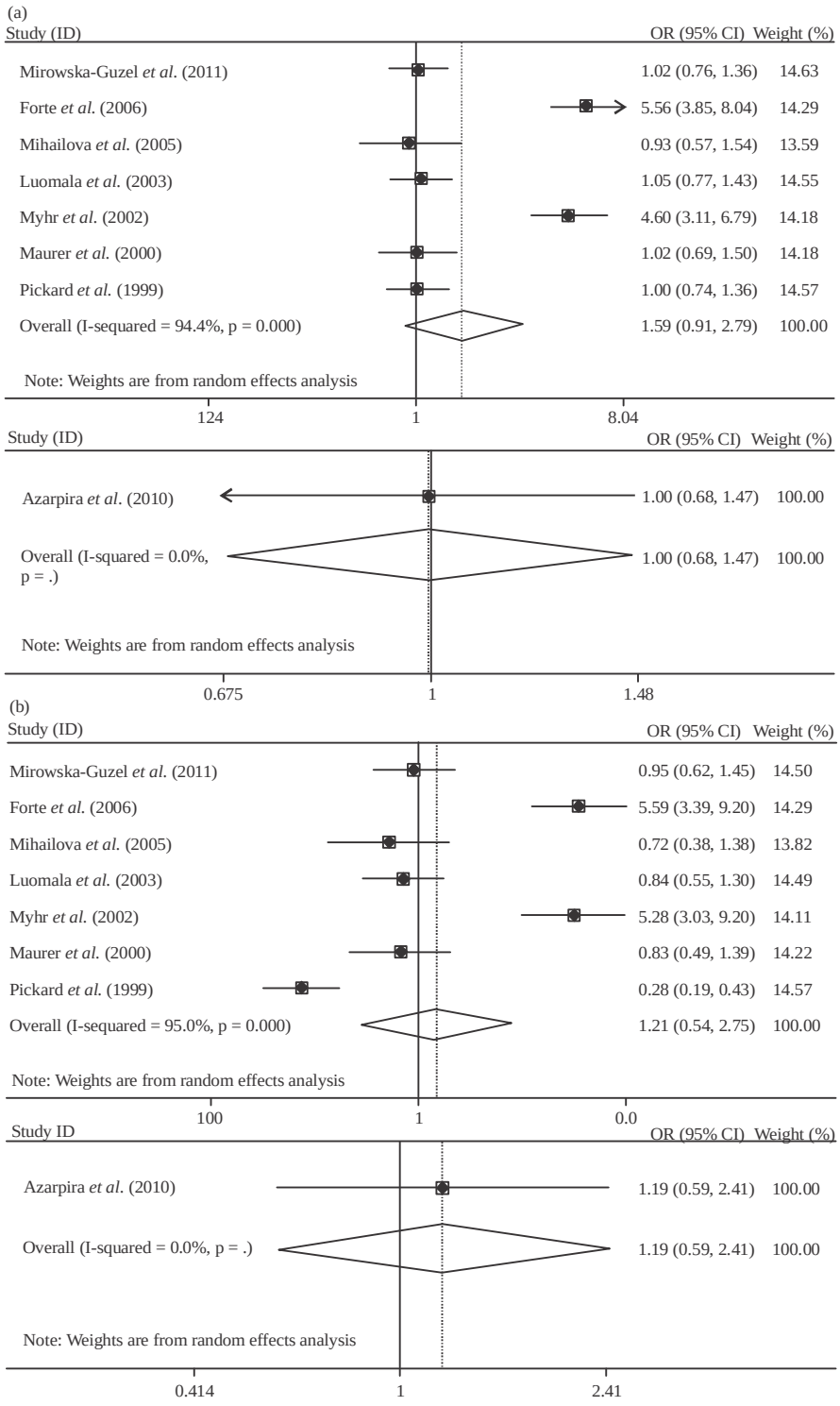

Fig. 3(a-d): Continue

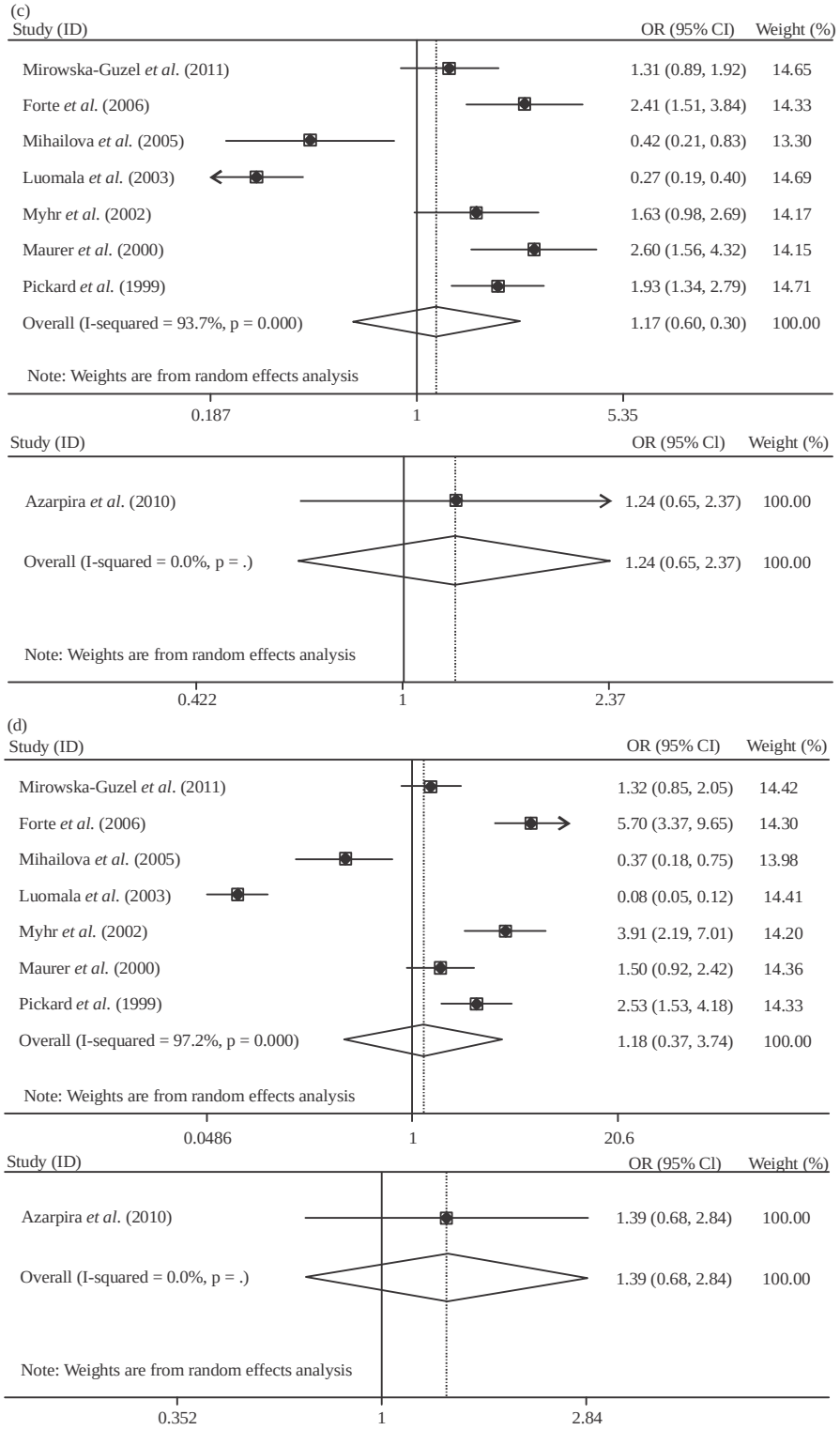

Fig. 3(a-d): Meta-analysis for the association between MS risk and the IL-10 -1082G/A polymorphism that stratified by ethnicity (Top, European, Down, Asian), (a) Dominant model, (b) Recessive model, (c) Heterozygote comparison and (d) Homozygote comparison

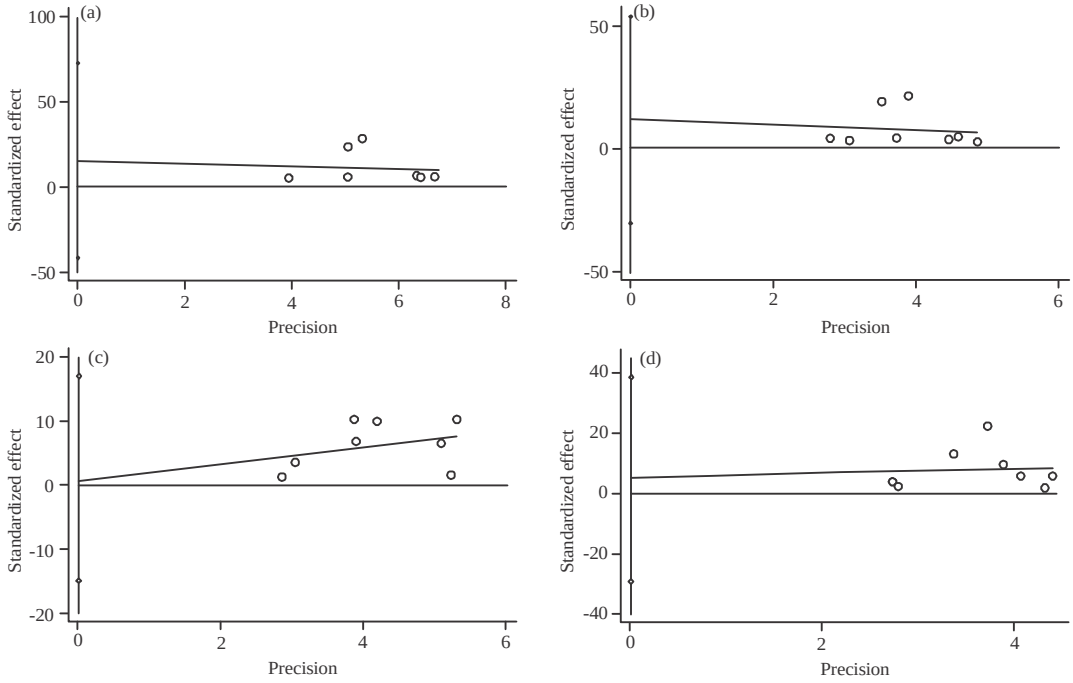

Fig. 4(a-d): Funnel plot for publication bias, (a) Dominant model, (b) Recessive model, (c) Heterozygote comparison and (d) Homozygote comparison

Publication bias: Begg's funnel plot and Egger's test were carried out to assess the publication bias of the literature. The shapes of the funnel plots are shown in Fig. 4.

Sensitivity analysis: No significant associations were obtained after sequentially excluding five case-control studies (Luomala *et al*., 2003; Myhr *et al*., 2002) suggesting that these studies were responsible for the significant of association (data not shown).

DISCUSSION

Multiple Sclerosis (MS) is a chronic demyelinating disease with unknown etiology, which is considered as a chronic immune-mediated neurodegenerative disorder. Numerous evidences indicate that cytokines Single Nucleotide Polymorphisms (SNP) appear to play a crucial role in the development of MS. The IL-10, an important immunoregulatory cytokine, play an anti-inflammatory role in the CNS and may be involved in the pathogenesis of MS. Many genetic studies reported that the cytokine gene polymorphisms were associated with MS risk. Although, the results of these studies on MS susceptibility and disease progression are promising, taken together, inconclusive results were obtained. To approve the association between IL-10 (−1082 G/A) polymorphism and MS, we conducted a meta-analysis, in which the result showed a significant relationship between this polymorphism and MS risk.

The results indicated that individuals who carry variant A allele (dominant model: AA+AG) had a nearly 50% non-significant increased risk of MS. In the further subgroup analysis, findings indicated that there was a significant association between IL-10 (−1082 G/A) polymorphism and MS risk in Caucasian ethnicity (European), hence no association was found in Asians (Iran). These estimates may assume a sort of genetic diversity among ethnicities. Though, there was only a single

study performed in Asians (Iran), these are not promising results for such ethnicity. It is widely accepted that MS is a complex demyelinating disease and both environmental and genetic factors contributed to its susceptibility and progression (Brooks *et al*., 2010; Lauer, 2010; Libbey *et al*., 2007; Maya *et al*., 2008; Sospedra and Martin, 2005; Stridh *et al*., 2014; Williams *et al*., 1991; Zivadinov and Pirko, 2012). Environmental factors comprise ethnicity, age, gender, diet, family history, parent-of-origin and so on. The new insight is the interaction between genetic and environmental factors and between several environmental factors as well. This may lead to new methods for prevention and possibly, for the treatment of MS.

This meta-analysis suffer from some limitations including, because of the lack of original information for each individual study, the stratification was not performed by other variables, such as, gender and age. Besides, only a single study was included in Asians, so the association needs to be confirmed in other ethnicities, such as Asians and Africans.

In conclusion, this meta-analysis provided evidence that IL-10 (−1082G/A) polymorphism is associated with a non-significant increased risk of MS, especially in Europeans. Current knowledge is not sufficient to explain the role of the aforementioned polymorphisms in MS pathogenesis. However, further large and well-designed studies are needed to confirm these findings, especially in other ethnicities, such as Asians and Africans.

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