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The change of Th17/Treg cells and IL-10/IL-17 in Chinese children with Henoch–Schonlein purpura

A PRISMA-compliant meta-analysis

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Abstract

Background: To date, the relationship of Th17 and Treg cells to Henoch–Schonlein purpura (HSP) in children remains controversial. Therefore, a systematic review and meta-analysis was conducted to reveal the potential role of the Th17 and Treg cells in children in acute stage of HSP.

Methods: PubMed, Embase, Web of Science and China National Knowledge Internet (CNKI) were systematically searched for eligible studies up to November 03, 2017. Quality assessment was carried out according to the modification of the Newcastle-Ottawa Scale (NOS). The data were analyzed by Stata SE12.0 (StataCorp, College Station, TX). Standard mean difference (SMD) with 95% confidence intervals (CI) was calculated continuous data.

Results: A total of 25 eligible studies were identified after a thorough literature search. The pooled results of the meta-analysis showed that values of Th17 frequency (SMD = 2.60; 95% CI: 1.98 to 3.23; $P < .0001$; $I^2 = 90.3\%$, $P < .0001$) and IL-17 level (SMD = 3.53; 95% CI: 2.71 to 4.35; $P < .0001$; $I^2 = 95.6\%$, $P < .001$) were significantly higher in children with HSP as compared to healthy children. In contrast, our analysis showed significant lower values of Treg frequency (SMD = -2.86; 95% CI: -3.53 to -2.19; $P < .001$; $I^2 = 92.4\%$, $P < .001$). However, no significance of IL-10 level was observed between children with HSP and healthy children (SMD = -1.22; 95% CI: -2.78 to 0.33; $P < .01$; $I^2 = 95.9\%$, $P < .001$).

Conclusion: In conclusion, our meta-analysis indicated that increased frequency of Th17 cells and level of IL-17, but lower frequency of Treg cells are associated with HSP in childhood. Considering the limitations of this meta-analysis, large-scaled studies need to be conducted to validate the current results.

Abbreviations: CI = confidence intervals, CNKI = China national knowledge internet, HSP = Henoch–Schonlein purpura, SMD = standard mean difference, Th17 = CD4+ T helper 17 cells, Treg = CD4+ CD25+ regulatory T cells.

Keywords: Henoch–Schonlein purpura (HSP), meta-analysis, Th17, Treg

1. Introduction

Henoch–Schonlein purpura (HSP) is a disease of the skin, gastrointestinal tract, joints and kidneys that most commonly affects children. More than 90% of patients are under 10 years of age, with a mean age of 6 years.[1] Recent studies suggest that HSP is related to inflammation and disordered immune response.[2,3] Several proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-8 may be involved in the pathogenesis of HSP.[3–5] However, the etiology and pathogenesis of HSP have not been completely understood.

$CD4^+$ T helper 17 cells (Th17) are a new subset of pro-inflammatory T helper cells defined by their production of interleukin 17 (IL-17).[6] Th17 cells play a critical role in the pathogenesis of serious autoimmune diseases, such as psoriasis, rheumatoid arthritis, multiple sclerosis and inflammatory bowel diseases.[7–10] The $CD4^+$ $CD25^+$ regulatory T cells (Treg) are a subpopulation of T cells and subset distinct from Th1 and Th2 cells, which modulate the immune system, maintain tolerance to self-antigens, and prevent autoimmune disease. Treg cells releases anti-inflammatory cytokines, IL-10 and transforming growth factor (TGF)-β1, to exert their anti-inflammatory properties.[11] Previous studies suggested that the imbalance between Th17 cells and Treg cells is important in the development of inflammatory and autoimmune diseases.[12] It has recently been shown that the proportions of Th17 cells were increased significantly in HSP children than in healthy controls.[13,14] In addition, the Th17/Treg imbalance may be involved in the pathogenesis of HSP.[14,15] Additionally, although many studies have indicated that the Th17/Treg imbalance was closely related to the pathogenesis of HSP, the small sample sizes and the single-center setting of those studies restrict the generalizability of the findings. Therefore, it is very imperative to perform a meta-analysis to systematically evaluate the relationship between the Th17/Treg imbalance and the children with HSP.

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2. Materials and methods

This study is a systematic review, and does not involve individual data. Thus, it does not need approval of ethics committee.

2.1. Literature search

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16,17] PubMed, Embase, Web of Science and China National Knowledge Internet (CNKI) were comprehensively searched for eligible studies to November 03, 2017. No restrictions on publication date, type or language were applied to identify publications. The Search strategy was determined by the combination terms including "Th17 cells", "IL-17", "Treg cells", or "IL-10", and "Henoch–Schonlein purpura". The reference lists of retrieved articles were manually screened to determine whether they should be included.

2.2. Study selection

The studies included in the present meta-analysis had to follow the criteria:

(1) compared the outcomes of frequency of Th17 cells and Treg cells investigated in HSP children;
(2) written in English or Chinese.

In contrast, the exclusion criteria included the following aspects:

(1) duplicate of a previous publication;
(2) studies were published as Editorials, case reports, conference abstracts;
(3) animal experiment.

2.3. Data extraction and quality assessment

Data from the included studies were extracted by 2 independent investigators. Any inconsistency between the investigators was resolved by the third reviewer. Study and patient baseline characteristics including name of first authors, year of publication, study design, simple size, age range of patients, sex of patients, frequency of Th17 cells, levels of IL-17, frequency of Treg cells, and levels of IL-10.

The modified 9-star Newcastle–Ottawa scale (NOS) was applied to evaluate the quality of studies, in which patient selection, comparability exposure, and assessment of outcome were scored respectively and then these scores were added up to get a total score.[17] The maximum total score obtained by this scoring system was 9, and studies with scores ≥ 7 were defined as high quality.

2.4. Statistical methods

In the present meta-analysis, all data were pooled using stata SE12.0 (StataCorp, College Station, TX). Standard mean difference (SMD) with a 95% CI was used to analyze continuous variables. Heterogeneity across the included studies was estimated based on I^2, with $I^2 > 50\%$ regarded as significant heterogeneity. If outcomes were associated with significant heterogeneity, a random-effects model was used to minimize bias.

To assess the sources of heterogeneity or to confirm the stability of pooled estimation of outcomes, a sensitivity analysis was performed. The results were considered statistically significant at 2-sided P values $< .05$. Publication bias was assessed by funnel plots and Begg and Egger test.[18,19] Duval nonparametric trim-and-fill method was used to evaluate the potential effect of publication bias,[20] if significant publication bias exists.

3. Results

3.1. Study selection and study characteristics

The study screening and selection processes were shown in the flowchart reported in Figure 1. We identified 108 publications, with 21 from PubMed, 32 from Embase, 26 from Web of science, and 39 from China National Knowledge Internet (CNKI). After 7 duplicates were removed, 101 studies were checked by screening title and abstract by 2 investigators. Then a total of 63 full texts remained after excluding the studies on irrelevant topics (n = 58), review article and comments (n = 5). Then we further reviewed the full texts of those remained publications. Subsequently, 4 conference abstracts and 16 studies with no data of interest were excluded, at last, with 25 articles included in the present meta-analysis.[2,13,14,21–43] Among all the included studies, 24 were retrospective studies and 1 were case-control analysis. The main baseline characteristics of the included publications are at length provided in Table 1 and Table 2.

3.2. Quality judgments of studies

The scores obtained according to the modification of the Newcastle–Ottawa scale ranged from 5 to 7 (Table 1). All of the included studies were awarded at least 6 points except that one study obtained 5 points, which were judged as moderate quality. In particular, 5 studies were awarded 7 points, and judged as high-quality.

3.3. The results of meta-analysis

3.3.1. Values of Th17 frequency and IL-17 level in children with HSP. The pooled random-effects SMD estimate showed significant higher values of Th17 frequency (SMD = 2.60; 95% CI: 1.92 to 3.23; $P < .0001$; $I^2 = 93.0\%$, $P < .0001$) in children with HSP as compared to healthy children (Fig. 2). The result also showed significant higher values of IL-17 level (SMD = 3.53; 95% CI: 2.71 to 4.35; $P < .0001$; $I^2 = 95.6\%$, $P < .001$) in children with HSP as compared to healthy children (Fig. 3).

3.3.2. Values of Treg frequency and IL-10 level in children with HSP. The pooled SMD indicated lower values of Treg frequency (SMD = -2.86; 95% CI: -3.53 to -2.19; $P < .01$; $I^2 = 92.4\%$, $P < .001$) in children with HSP as compared to healthy children (Fig. 4). However, the pooled SMD suggested no statistically different values of IL-10 level (SMD = -1.22; 95% CI: -2.78 to 0.33; $P = .09$; $I^2 = 95.9\%$, $P < .001$) in children with HSP as compared to healthy children (Fig. 5).

3.3.3. Sensitivity analysis. Sensitivity analysis was conducted by removal of single study in each step. As Figures 6–8 showed, respectively, the pooled analysis of Th17, IL-17 and Treg did not alter significantly when any study was omitted, which indicated that our pooled results were robust. The Sensitivity analysis for the pooled result of IL-10 was not performed due to the limitation of the number of eligible studies.

3.4. Publication bias

The publication bias for the pooled results of Th17, IL-17 and Treg values using the Begg funnel plot and Egger tests, but the

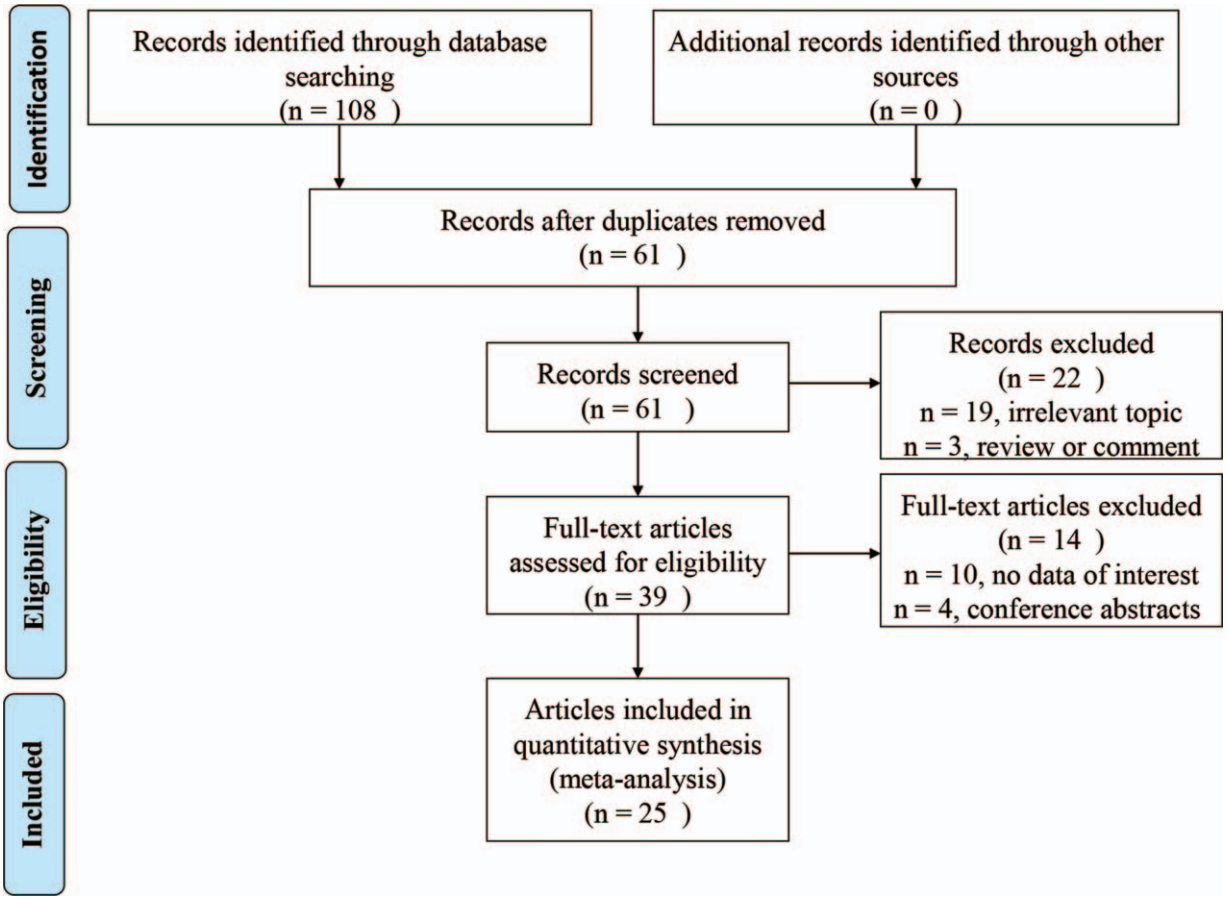

Figure 1. Flow diagram of study selection.

Table 1

The main characteristic of the included studies.

Author	Year	Study design	Simple size		Age, year		Sex Male/Female		NOS
			Healthy	HSP	Healthy	HSP	Healthy	HSP	
Chang	2016	R	42	30	6.5	6.7	25/17	20/10	6
Chen	2013	R	18	23	6.8	6.2	10/8	14/9	6
Fan	2010	R	30	40	9.8	10.7	18/12	24/16	7
Gao	2014	R	15	42	7.0	7.5	8/7	22/20	5
Huang	2014	R	25	25	NR	8.7	NR	13/12	7
Jen	2011	R	30	30	NR	7.3	NR	15/15	7
Li	2014a	R	30	30	6.21	5.93	15/15	17/13	6
Li	2014b	R	20	30	7.50±2.54	8.50±2.86	11/9	16/14	5
Liang	2015	R	30	30	NR	NR	16/14	24/17	7
Liu	2015	R	30	30	8.93±3.1	8.9±2.8	17/13	16/14	6
Liu	2014	R	30	78	28.6±4.4	28.4±4.5	17/13	44/34	7
Liu	2012	R	30	54	7.2	7.5	18/12	34/20	6
Ma	2010	R	38	59	10.13±3.31	10.42±3.60	19/19	29/30	7
Meng	2011	R	20	60	7.58±1.56	7.79±2.31	10/10	34/26	6
Miao	2014	R	30	30	NR	NR	15/15	17/13	6
Tan	2017	R	16	15	7.6±2.8	NR	9/7	NR	6
Wang	2015a	R	40	40	4.5	5.0	24/16	27/13	6
Wang	2015b	R	30	35	NR	NR	16/14	20/15	7
Xiao	2014a	R	22	39	8.2	7.4	12/10	23/16	7
Xiao	2014b	R	40	42	10.5±4.8	10.6±4.8	20/20	22/20	6
Xing	2017	R	35	68	5	4	20/15	40/28	6
Yang	2006	R	20	20	NR	NR	10/10	12/8	6
Zhang	2015	R	30	52	7.61±3.8	7.28±4.0	16/14	30/22	6
Zhang	2016	R	30	35	8.56	8.31	17/13	22/13	7
Zi	2014	R	30	42	6.5	6.7	20/10	25/17	6

HSP = Henoch-Schonlein Purpura, NR = not reported, R = Retrospective design.

Table 2

values of Th17 frequency, Treg frequency, Levels of IL-17 and Levels of IL-10 in HSP patients and healthy controls.

	Th17 frequencies (%)				Treg frequencies (%)				Levels of IL-17 (ng/L)				Levels of IL-10 (ng/L)			
	Healthy		HSP		Healthy		HSP		Healthy		HSP		Healthy		HSP	
First author	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Chang 2016	NR	NR	NR	NR	NR	NR	NR	NR	11.09	1.77	13.17	2.84	NR	NR	NR	NR
Chen 2013	0.7	0.1	1.7	0.3	3.8	0.2	2.3	0.3	30.31 ng/L	2.31	80.81	3.56	20.27	1.83	11.04	1.61
Fan 2010	1.19	1.31	2.97	1.57	NR	NR	NR	NR	10.39	2.7	24.57	3.57	NR	NR	NR	NR
Gao 2014	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	11.84	4.82	14.90	4.43
Huang 2014	0.49	0.08	0.76	0.16	8.73	0.60	5.68	0.95	24.0	1.02	30.73	3.36	NR	NR	NR	NR
Jen 2011	0.71	0.15	1.67	0.36	NR	NR	NR	NR	47.7	22.6	281.2	91.4	NR	NR	NR	NR
Li 2014 a	1.20	0.23	2.30	0.55	12.20	3.95	9.41	1.43	15.20	2.49	23.36	6.04	NR	NR	NR	NR
Li 2014b	0.84	0.41	2.14	0.90	NR	NR	NR	NR	10.59	4.17	38.36	13.44	NR	NR	NR	NR
Liang 2015	0.27	0.10	0.41	0.16	9,79	0.99	5.37	1.98	105.00	17.43	311.32	29.77	NR	NR	NR	NR
Liu 2015	0.52	0.07	0.71	0.14	8.81	0.59	5.68	1.00	22.14	5.05	32.03	6.26	NR	NR	NR	NR
Liu2014	NR	NR	NR	NR	23.8	4.95	11.78	6.31	NR	NR	NR	NR	NR	NR	NR	NR
Liu2012	NR	NR	NR	NR	3.93	0.42	2.25	1.02	29.75	21.65	86.65	13.90	NR	NR	NR	NR
Ma 2010	0.39	0.15	1.87	0.56	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Meng 2011	NR	NR	NR	NR	4.57	0.85	3.88	0.98	NR	NR	NR	NR	NR	NR	NR	NR
Miao 2014	0.59	0.27	1.73	0.68	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tan 2017	0.77	0.05	1.23	0.11	3.64	0.16	2.97	0.20	NR	NR	NR	NR	NR	NR	NR	NR
Wang 2015a	NR	NR	NR	NR	NR	NR	NR	NR	20.23	10.70	40.40	11.81	NR	NR	NR	NR
Wang 2015b	0.25	0.12	0.37	0.28	10.91	1.11	5.37	3.26	105.00	17.43	311.32	29.77	NR	NR	NR	NR
Xiao 2014a	NR	NR	NR	NR	NR	NR	NR	NR	14.80	3.42	21.71	4.20	10.87	3.22	11.53	4.50
Xiao 2014b	1.62	0.44	6.45	1.62	NR	NR	NR	NR	6.26	2.54	38.83	9.12	NR	NR	NR	NR
Xing 2017	0.59	0.18	2.98	0.51	5.45	2.61	0.97	0.14	4.74	0.89	27.34	3.97	NR	NR	NR	NR
Yang 2006	NR	NR	NR	NR	10.92	2.15	6.90	1.60	NR	NR	NR	NR	NR	NR	NR	NR
Zhang 2015a	0.54	0.28	1.20	0.41	5.95	0.45	2.29	0.67	7.01	4.04	24.16	12.31	95.72	37.06	68.82	24.33
Zhang 2016	0.66	0.26	1.35	0.46	3.15	0.67	1.81	0.46	16.86	6.22	34.58	9.01	NR	NR	NR	NR
Zi 2014	NR	NR	NR	NR	NR	NR	NR	NR	11.09	1.77	13.17	2.84	NR	NR	NR	NR

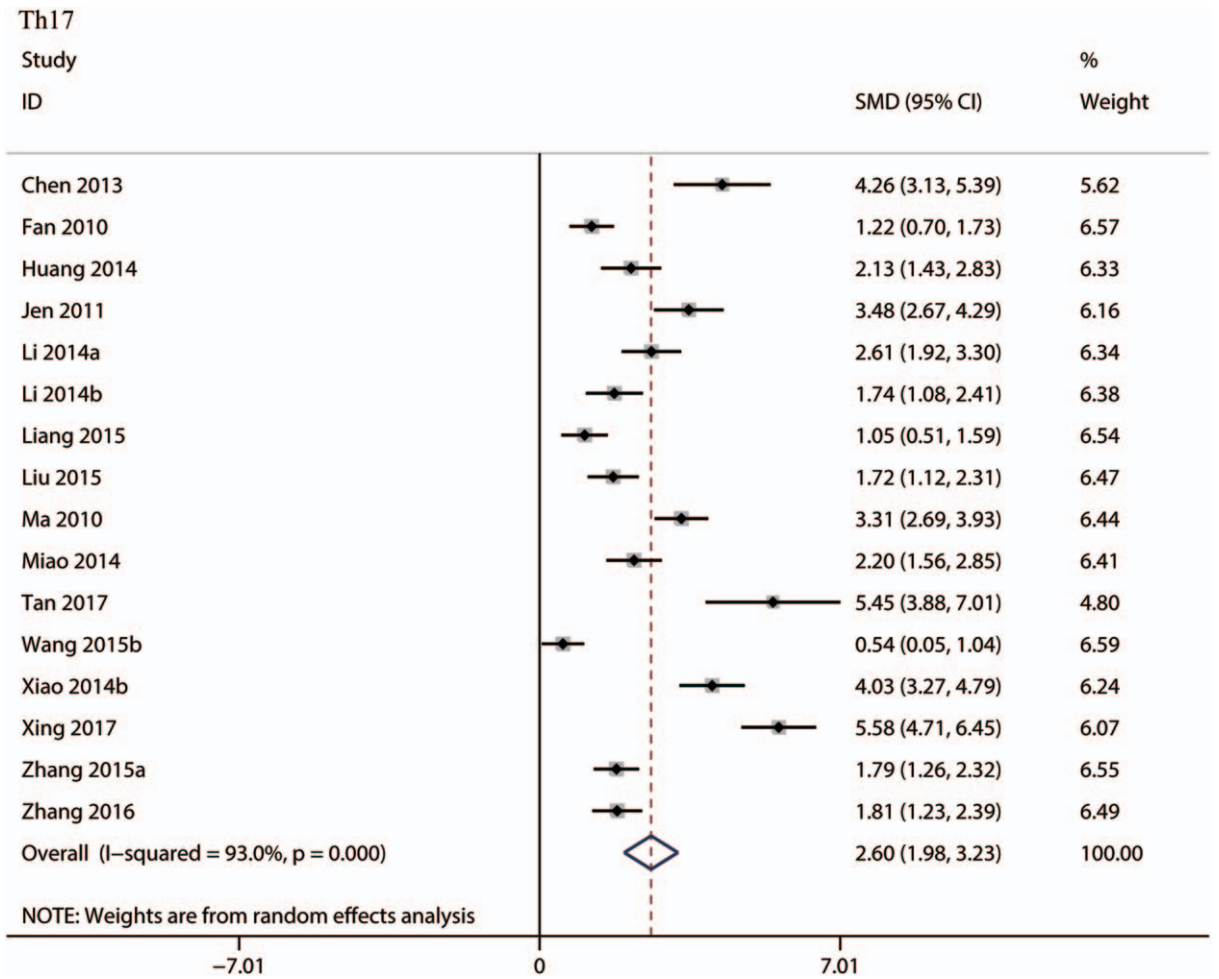

Figure 2. The meta-analysis of values of Th17 frequency in children with HSP.

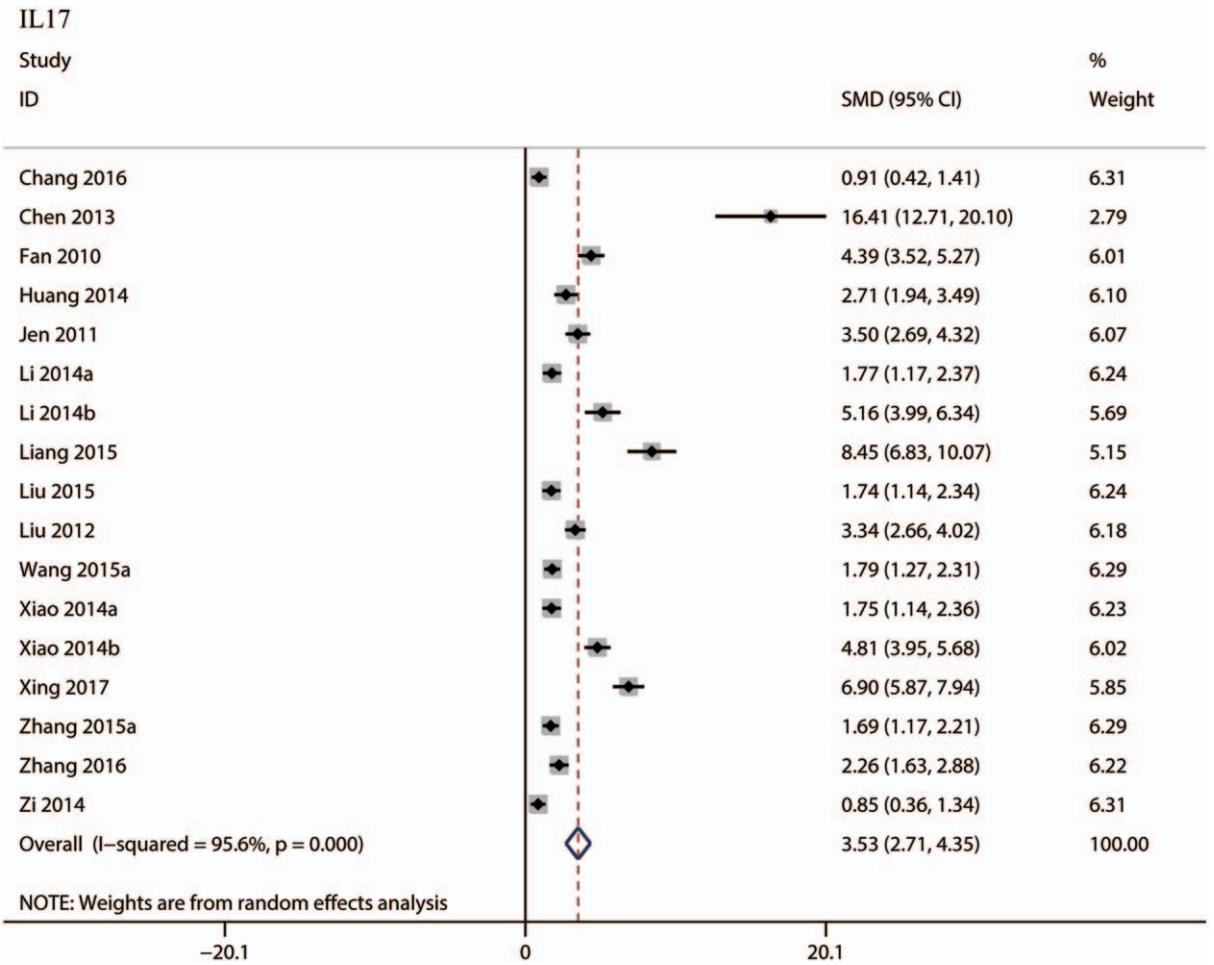

Figure 3. The meta-analysis of values of IL-17 level in children with HSP.

assessment of publication bias for the pooled result of IL-10 was not conducted due to the limitation of the number of eligible studies. From the results, significant publication biases were detected for the pooled results of Th17, IL-17 and Treg, which were reflected by Z value (Z = 3.69, 4.90 and 3.28) and *P* value (*P* < .001, *P* < .001 and *P* = .001) from Begg test, as well as t value (t [bias] = 5.12, 9.72 and -4.82) and *P* value (*P* < .001, *P* < .001 and *P* < .001) from Egger test. Furthermore, the asymmetry of the funnel plots for the pooled results of Th17, IL-17 and Treg also indicated the existence of significance publication biases, as in Figures 9–11 showed respectively. Then, the "trim and fill method" was applied to figure out whether the significant publications substantially influence the stability of our pooled results. From the results of "trim and fill method" analysis, we found that the adjusted pooled SMDs of Th17, IL-17, and Treg did not change significantly and the funnel plots also became relatively symmetric (Figs. 12–14), which indicated that the publication bias did not significantly impact the reliability of our pooled results of Th17, IL-17, and Treg values.

4. Discussion

To the best of our knowledge, this is the first meta-analysis to investigate the difference of Th17 frequency, IL-17 level, Treg frequency and IL-10 level between HSP children and healthy children. Our study found that the frequency of Th17 cells and the level of IL-17 were higher in HSP children than in healthy controls. In contrast, the frequency of Treg cell was lower in HSP children than in the healthy controls. These results indicate that a Th17/Treg cell imbalance exists in HSP children, and it appears to closely correlate with disease activity.

HSP is the most common type of connective tissue diseases and its pathogenesis remains unknown. Recently, many investigators have evaluated the balance of Th17/Treg and reported an imbalance in patients with various autoimmune and inflammatory diseases. Numerous studies in the past revealed that expression levels of proinflammatory cytokines, such as IL-6 and IL-8, were elevated in patients with HSP.[44,45] It has recently been shown that the increased frequency of Th17 cells and IL-17 level in childhood HSP may in part contribute to vascular inflammation.[2] Th17 cells mediate the pathology in the inflammation and autoimmune tissue injury through recruiting other inflammatory cell types and cytokines. Some studies have reported that several cytokines, such as TGF-β and IL-21, can induce Th17 cell differentiation, and these cytokines and Th17 cells appear to contribute to the clinical outcome of autoimmune diseases.[46,47] Th17 cells can induce inflammation and autoimmune tissue injury through expressing retinoic acid-related orphan receptor γt.[48] Previous studies suggested that Th17 cells involved in the development of autoimmunity through the production of IL-17 and IL-6.[49] Recent study has reported that IL-17 can stimulate monocytes/macrophages, smooth muscle

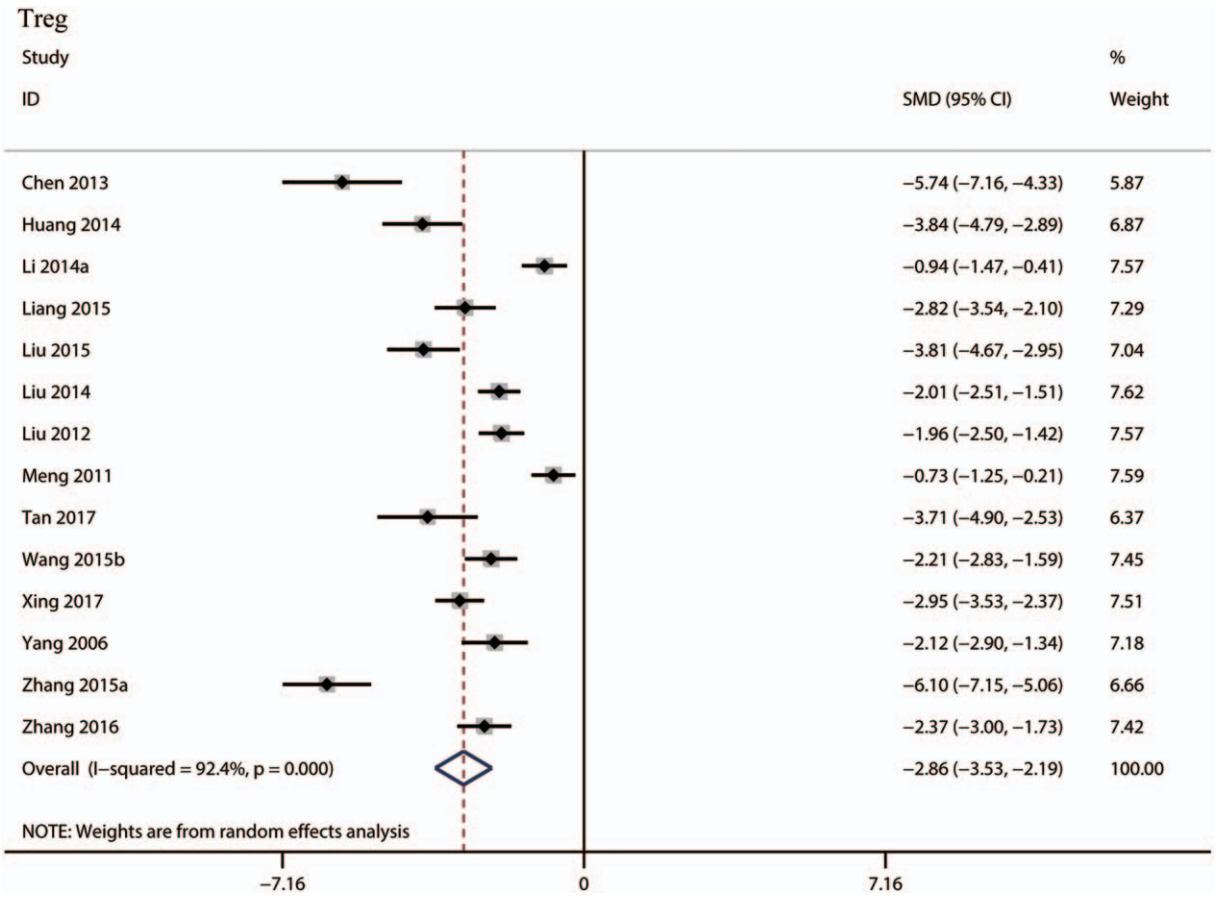

Figure 4. The meta-analysis of values of Treg frequency in children with HSP.

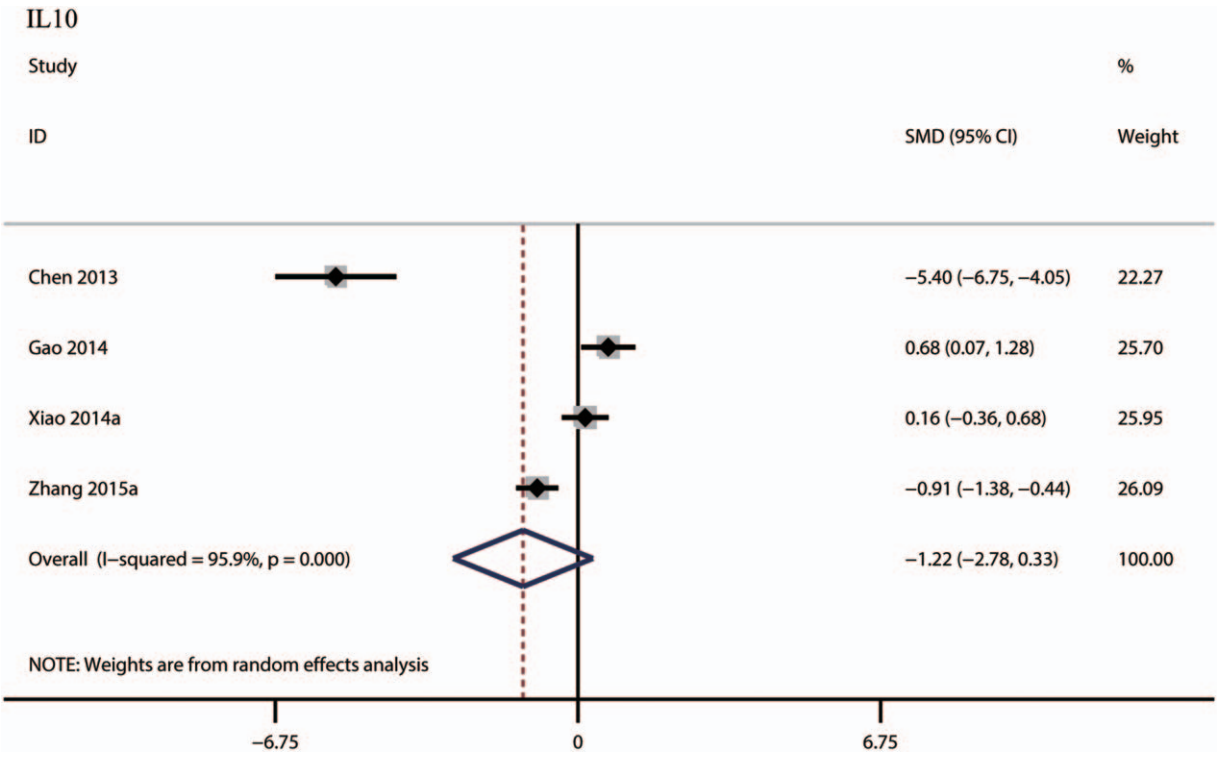

Figure 5. The meta-analysis of values of IL-10 level in children with HSP.

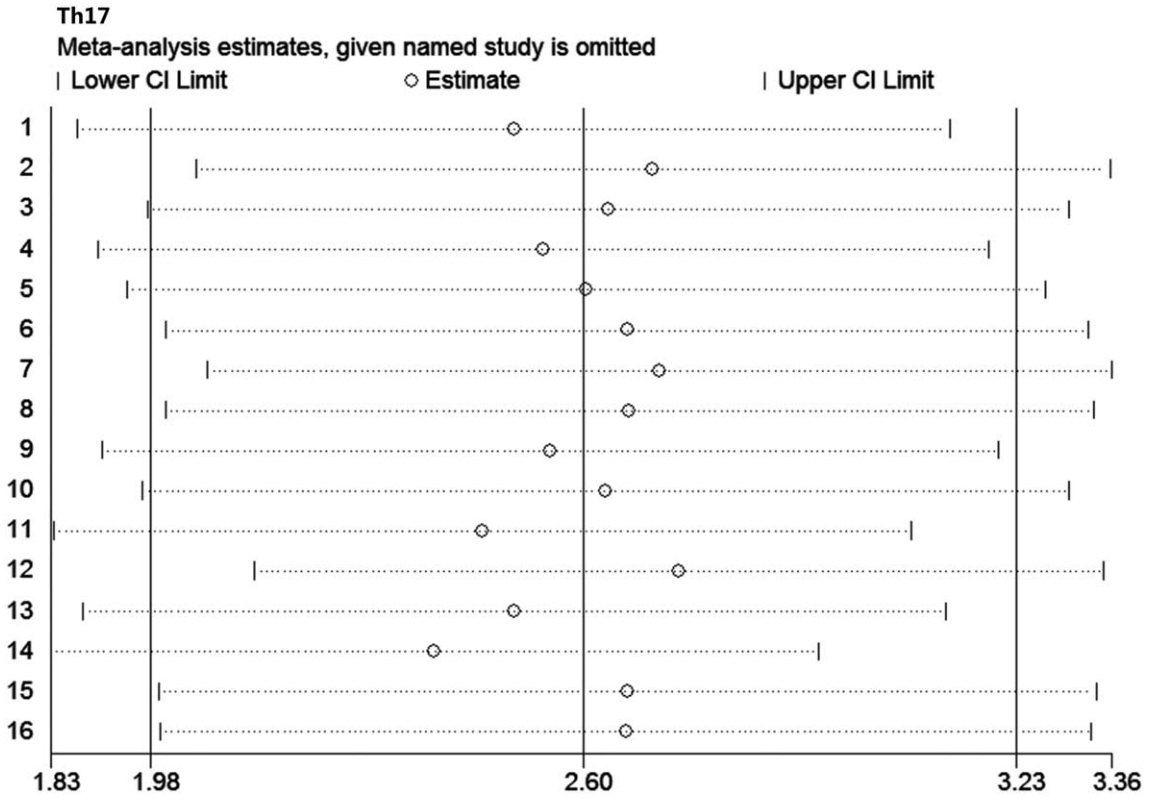

Figure 6. Sensitivity analysis of the pooled values of Th17 frequency in children with HSP.

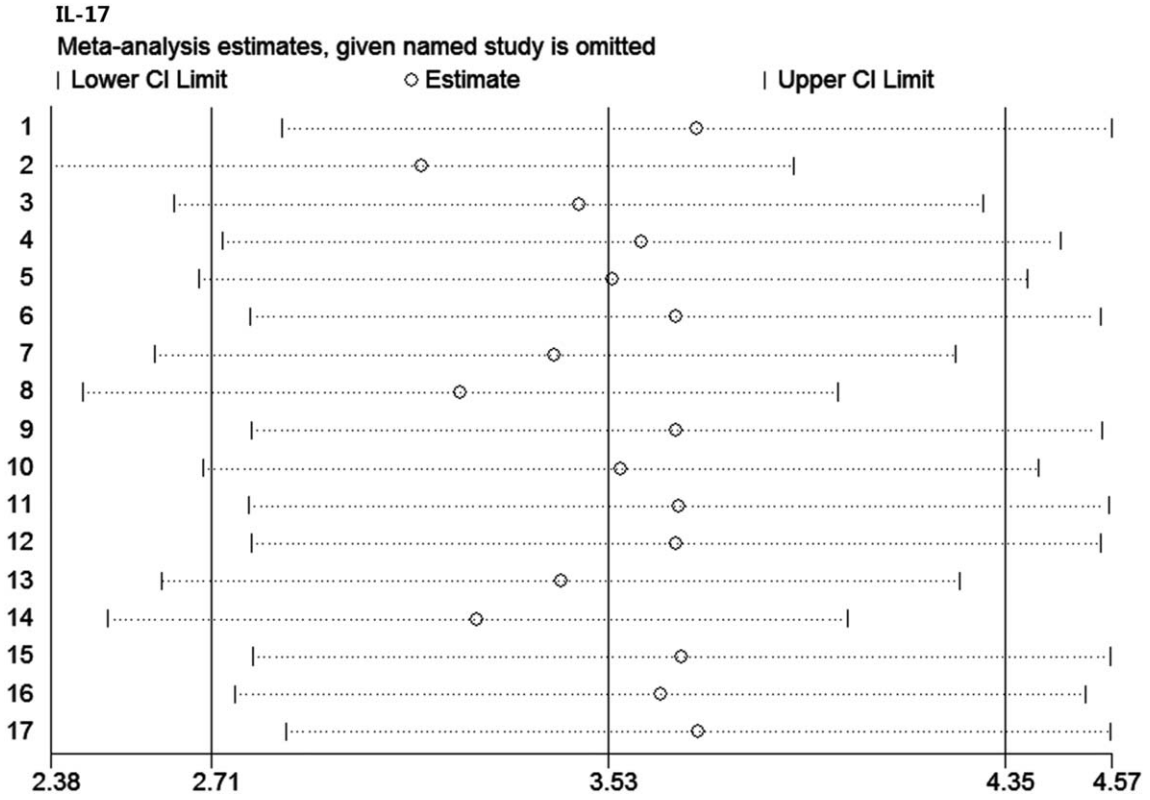

Figure 7. Sensitivity analysis of the pooled values of IL-17 level in children with HSP.

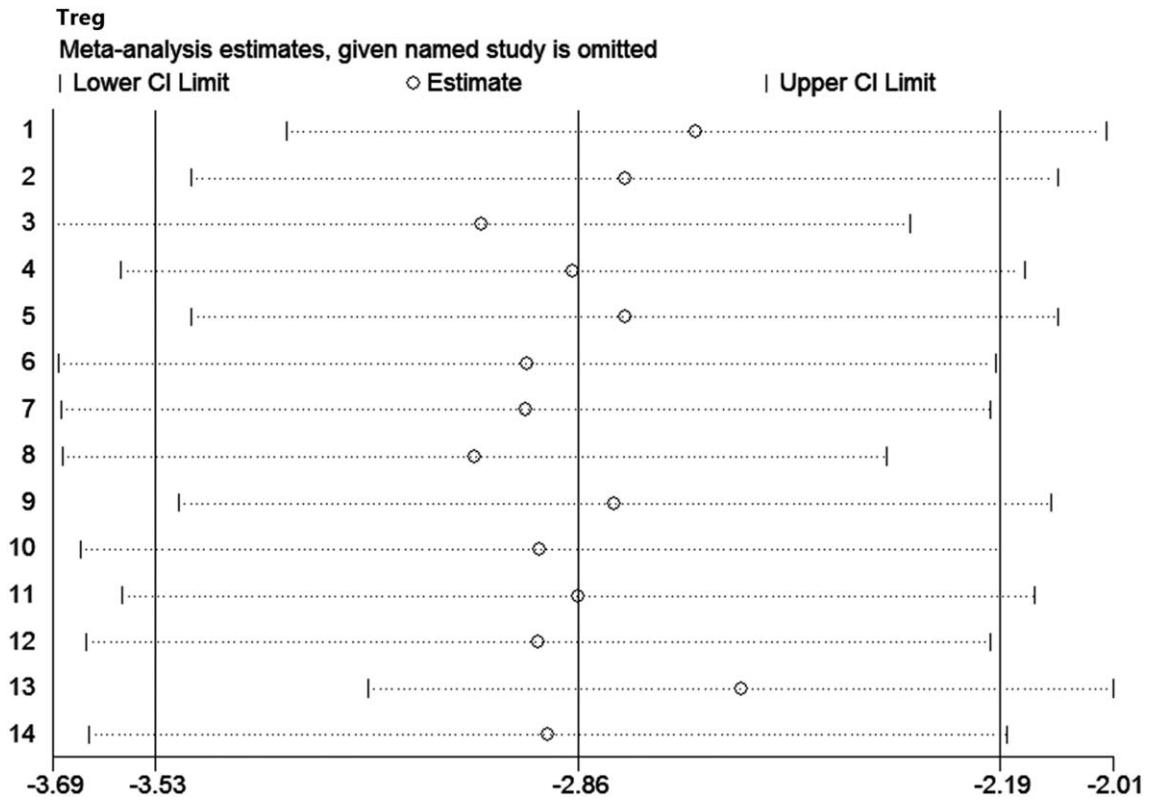

Figure 8. Sensitivity analysis of the pooled values of Treg frequency in children with HSP.

cells, epithelial cells and endothelial cells to enhances the expression of chemokines and inflammatory cytokines and promotes polymorphonuclear neutrophil recruitment to sites of inflammation.[50,51]

Treg cells plays a critical role in the maintenance of peripheral immunological tolerance by limiting the autoimmune process and inflammatory responses.[14] Treg cells secrete some anti-inflammatory cytokines, such as IL-10 and TGF-β1, to exert their function. The number of Treg cells have been suggested decreased in several autoimmune diseases.[52,53] Bettelli et al have reported that the Th17 and Treg cell populations are mutually regulated during differentiation.[54] Several proinflammatory cytokines,

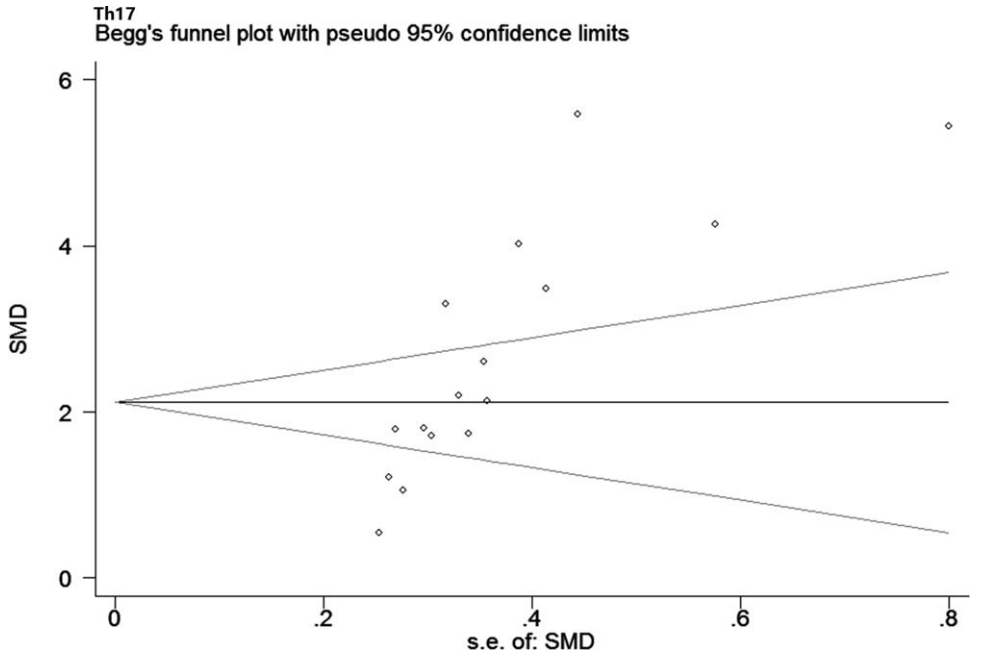

Figure 9. The funnel plot depicting the publication bias for the pooled values of Th17 frequency.

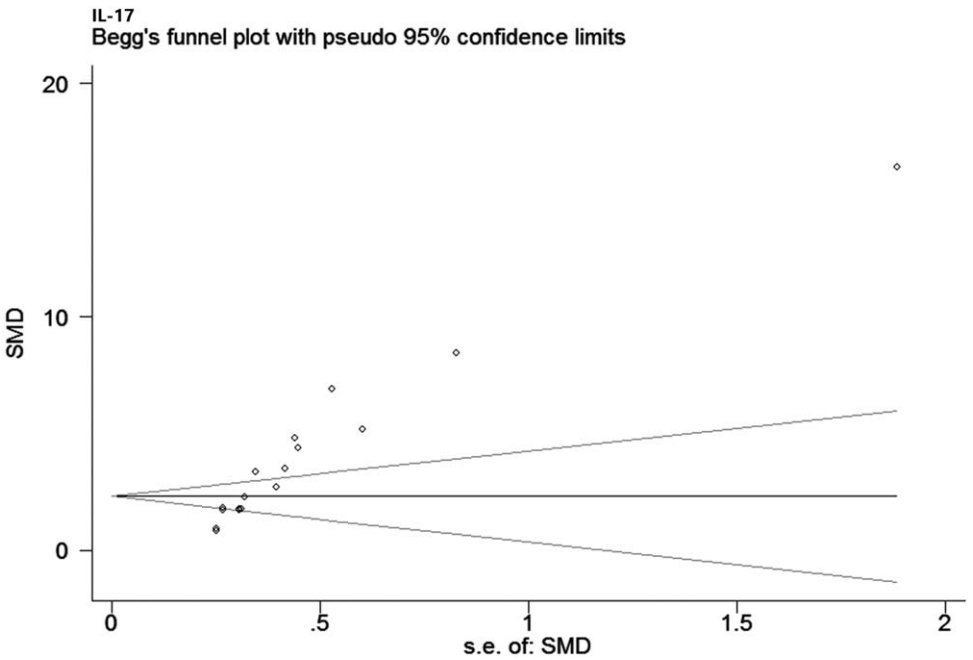

Figure 10. The funnel plot depicting the publication bias for the pooled values of IL-17 level.

such as IL-6 and IL-21, can regulatory Treg cells and induced IL-17 production in a TGF-β-dependent manner.[54] Through this way, the proinflammatory milieu could convert Treg cells to Th17 cells and shift the balance between the immune response and inflammation toward inflammation. Previous studies have suggested that the Th17/Treg imbalance is strongly associated with the pathogenesis of some immune inflammatory diseases.[55] As a result, an appropriate balance between Treg cells and Th17 cells can ensure the avoidance of autoimmunity and inflammatory reactions.

HSP is the most common childhood vasculitis, affecting 10 to 20 children per 100,000 per year. Our meta-analysis suggests that increased Th17/IL-17 and decreased Treg frequency is associated with HSP. This finding may be important for the management of HSP patients in clinical practice. For instance, regulating the Th17/Treg cell ratio might play a beneficial role in the treatment

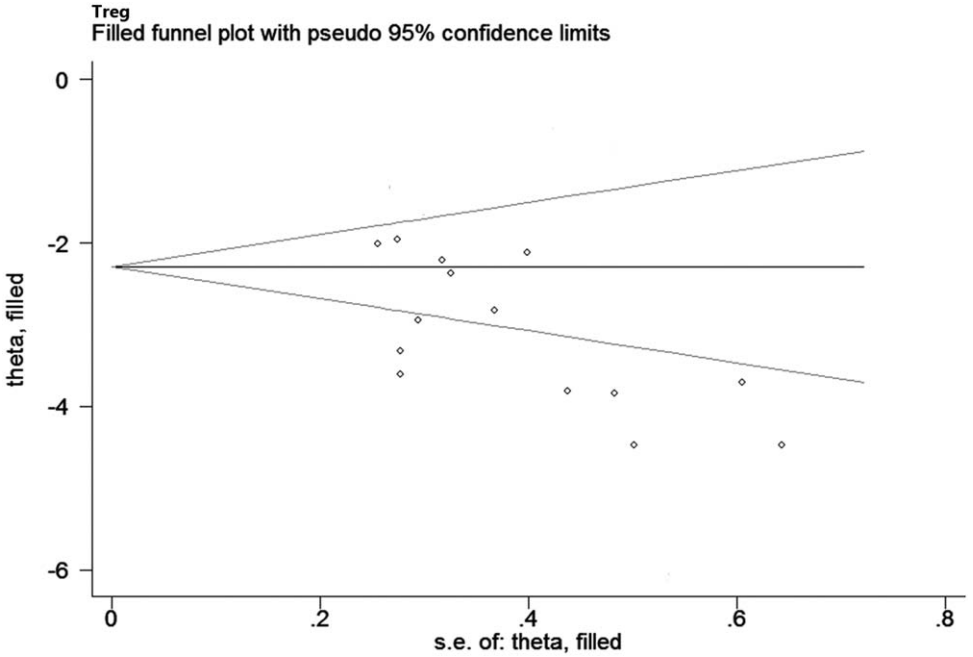

Figure 11. The funnel plot depicting the publication bias for the pooled values of Treg frequency.

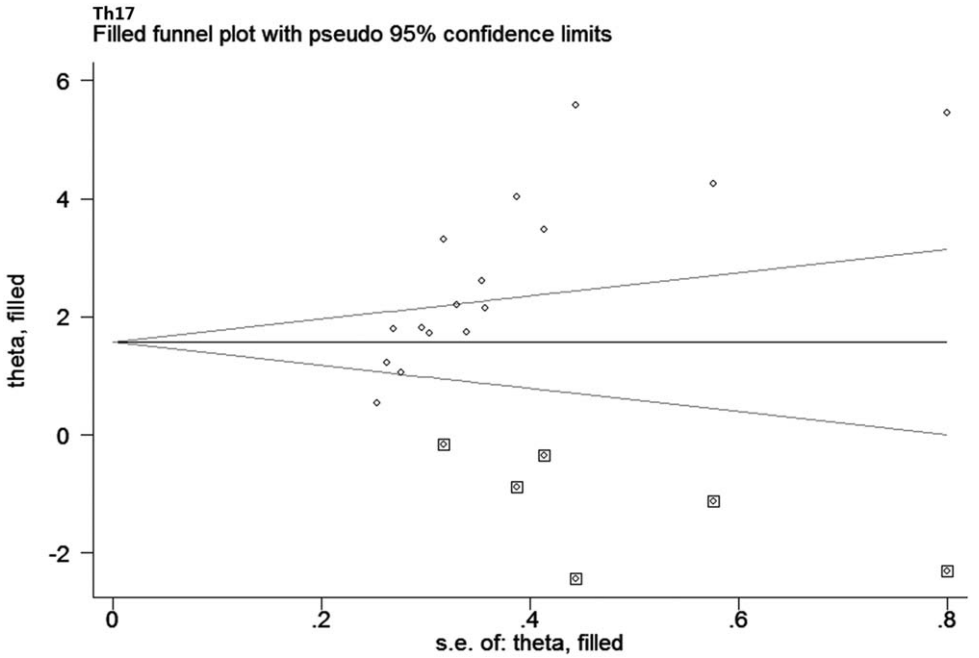

Figure 12. The adjusted funnel plot of Th17 frequency after the "trim and fill method" analysis.

of HSP. Recently, metformin, a common medicine to treat type 2 diabetes, was shown to attenuate some autoimmune diseases, such inflammatory bowel disease and autoimmune arthritis, by regulating the between Treg/Th17 balance.[56–58] Given the involvement of the between Treg/Th17 imbalance in HSP, metformin may be suitable for treating HSP patients. Of course, this hypothesis needs to be confirmed in future studies. Nevertheless, as to the management of HSP in clinical practice, it should be stressed that in most cases HSP is self-limiting and very little intervention is necessary. Therefore, the application of metformin may be only considered in cases in which there is significant concern about long-term renal function.

Overall, this meta-analysis demonstrates that there is close relationship between the Th17/Treg imbalance and the children with HSP. However, there are several limitations in our present meta-analysis. Firstly, the sample size in our study was relatively small, which might have led to statistical bias. Secondly, the results should be interpreted with caution as a result of obvious

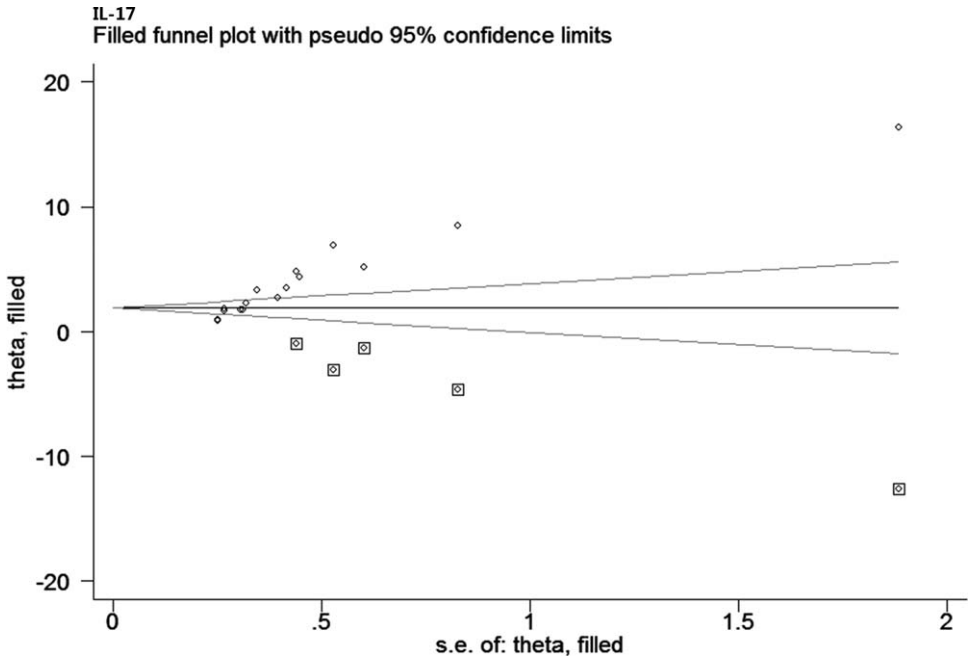

Figure 13. The adjusted funnel plot of IL-17 level after the "trim and fill method" analysis.

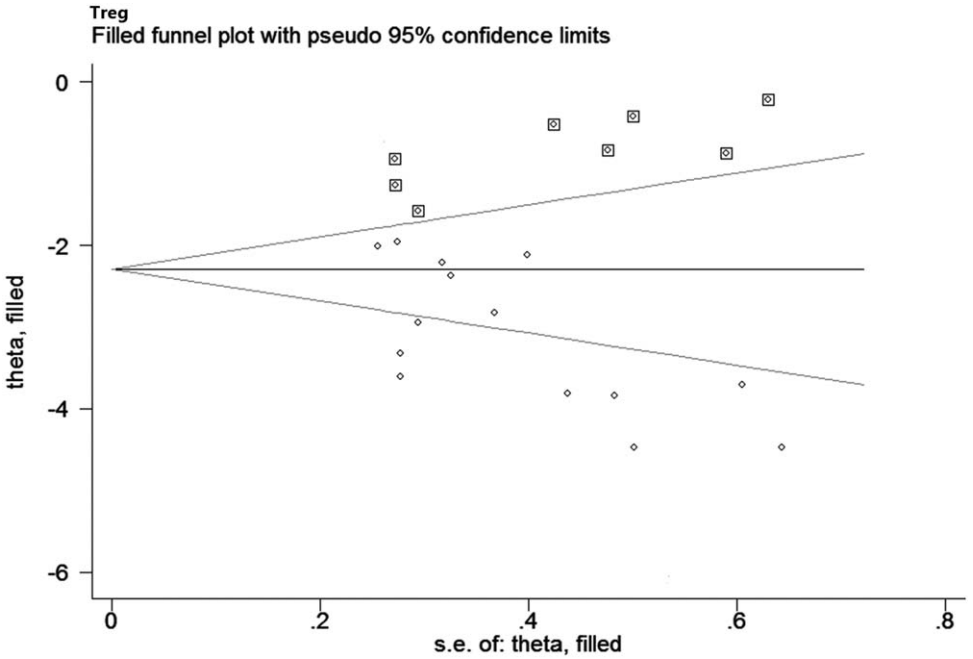

Figure 14. The adjusted funnel plot of Treg frequency after the "trim and fill method" analysis.

heterogeneity. Last but not least, the current meta-analysis did not investigate the relationship between Th17/Treg and other factors that influenced the development of HSP.

5. Conclusions

In conclusion, our meta-analysis indicated that increased frequency of Th17 cells and level of IL-17, but lower frequency of Treg cells are associated with HSP in childhood. Considering the limitations of this meta-analysis, large-scaled studies need to be conducted to validate the current results.

Author contributions

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