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Author(s)	Yamaguchi, Atsushi; Saito, Yoshitaka; Okamoto, Keisuke; Narumi, Katsuya; Furugen, Ayako; Takekuma, Yoh; Sugawara, Mitsuru; Kobayashi, Masaki
Citation	Supportive care in cancer, 29, 7747-7753 <a href="https://doi.org/10.1007/s00520-021-06359-7">https://doi.org/10.1007/s00520-021-06359-7</a>
Issue Date	2021-06-23
Doc URL	<a href="http://hdl.handle.net/2115/86173">http://hdl.handle.net/2115/86173</a>
Rights	This is a post-peer-review, pre-copyedit version of an article published in Supportive care in cancer. The final authenticated version is available online at: <a href="http://dx.doi.org/10.1007/s00520-021-06359-7">http://dx.doi.org/10.1007/s00520-021-06359-7</a>
Type	article (author version)
File Information	Revised Manuscript.pdf



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Preexisting autoimmune disease is a risk factor for immune-related adverse events: a meta-analysis

**Atsushi Yamaguchi<sup>1,2</sup>, Yoshitaka Saito<sup>1</sup>, Keisuke Okamoto<sup>1</sup>, Katsuya Narumi<sup>2</sup>, Ayako Furugen<sup>2</sup>, Yoh**

**Takekuma<sup>1</sup>, Mitsuru Sugawara<sup>1,3</sup>, Masaki Kobayashi<sup>2, 4,\*</sup>**

<sup>1</sup> Department of Pharmacy, Hokkaido University Hospital, Kita-14-jo, Nishi-5-chome, Kita-ku, Sapporo, 060-8648, Japan.

<sup>2</sup> Laboratory of Clinical Pharmaceutics & Therapeutics, Division of Pharmasciences, Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12-jo, Nishi-6-chome, Kita-ku, Sapporo 060-0812, Japan.

<sup>3</sup> Laboratory of Pharmacokinetics, Division of Pharmasciences, Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12-jo, Nishi-6-chome, Kita-ku, Sapporo, 060-0812, Japan.

<sup>4</sup> Education Research Center for Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12-jo, Nishi-6-chome, Kita-ku, Sapporo 060-0812, Japan.

\*To whom correspondence should be addressed: Laboratory of Clinical Pharmaceutics & Therapeutics,

Division of Pharmasciences, Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12-jo, Nishi-6-chome, Kita-ku, Sapporo 060-0812, Japan.

Tel/Fax: +81-11-706-3770; E-mail: masaki@pharm.hokudai.ac.jp

## **Abstract**

Purpose: Patients with preexisting autoimmune disease (PAD) are often excluded from clinical trials assessing immune checkpoint inhibitors (ICIs). Therefore, the safety of ICI therapy in patients with PAD remains unclear. Herein, we evaluated the incidence of immune-related adverse events (irAEs) in patients with PAD when compared with non-PAD patients.

Methods: We searched MEDLINE/PubMed, Web of Science, and Google Scholar for eligible studies from inception to January 2021. Observational studies reporting the incidence of irAEs in patients with and without PAD were included. We then performed a meta-analysis of eligible studies using forest plots. The primary endpoint of this study was the incidence rate of irAEs between patients with and without PAD.

Results: We identified three prospective and three retrospective studies involving 206 patients with PAD and 3078 patients without PAD. In the meta-analysis, 128 patients with PAD (62.1%) experienced irAEs, which occurred in 51.9% of non-PAD patients, resulting in an odds ratio (OR) of 2.14 (95% confidence interval [CI] 1.58-2.89). In the subgroup analysis, the incidence of irAEs was significantly higher in patients with PAD (OR = 2.19, 95% CI [1.55-3.08]). Furthermore, no significant heterogeneity or publication bias was detected, indicating that our meta-analysis could be generalized to clinical settings.

Conclusion: This meta-analysis demonstrated that PAD was a risk factor for irAE incidence. These results suggest that monitoring the occurrence of irAEs in patients with PAD is required to manage irAEs appropriately.

Keywords: immune checkpoint inhibitors (ICIs); immune-related adverse events (irAEs); preexisting autoimmune disease (PAD); meta-analysis

## **1. Introduction**

Immune checkpoint inhibitors (ICIs) have remarkable anticancer activity for treating several types of cancer [1]. ICIs block the immune system-mediated response toward tumors by interacting between cytotoxic T-lymphocyte-associated-4 (CTLA-4) and CD80/CD86, as well as between programmed cell death protein 1 (PD-1) and programmed cell death protein ligand 1 (PD-L1) [1]. To date, anti-CTLA-4 antibody (ipilimumab), anti-PD-1 antibodies (nivolumab and pembrolizumab), and anti-PD-L1 antibodies (atezolizumab, durvalumab, and avelumab) have been approved, and their clinical applications have dramatically expanded.

Despite the significant efficacy of ICIs, adverse events associated with ICIs, also known as immune-related adverse events (irAEs), have been reported [2, 3]. IrAEs are associated with the mechanism of ICI action and can involve multiple organs, including the skin, endocrine system, and gastrointestinal tract [4]. Typically, irAEs are mild, and ICI therapy can be continued in most cases. However, severe irAEs result in treatment discontinuation and reduce the quality of life. Therefore, adequate management of irAEs is required to maximize the benefits of ICI therapy [4, 5].

Although the pathophysiology of irAEs is not well understood, the underlying mechanisms could involve upregulation of the immune system, which, in turn, causes inflammation and autoimmunity, similar to autoimmune diseases such as rheumatoid arthritis, autoimmune thyroid disease, and inflammatory bowel disease [6]. Accordingly, several clinical trials have excluded these populations from study participation.

Hence, the efficacy and safety of ICIs in these patients remains unknown. Recently, a meta-analysis of observational studies assessing preexisting autoimmune disease (PAD) populations has reported that ICI treatments are effective and irAEs are often manageable [7]. However, the study included PAD single-arm studies and did not compare the incidence of irAEs between patients with and without PAD. Furthermore, only a few comparative studies have been reported, and the results obtained so far remain controversial.

Based on this background, in the present study, we aimed to reveal whether PAD induces irAEs, by performing a meta-analysis of observational studies that reported the incidence of irAEs, with and without PAD incidence.

## **2. Methods**

### *2.1. Study design*

We performed a meta-analysis according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [8]. The primary outcome of this meta-analysis was the incidence of irAEs between patients with and without PAD.

### *2.2. Data sources and searches*

We developed a search strategy to identify related records, with no language restriction, for MEDLINE/PubMed, Web of Science, and Google Scholar, from database inception to January 31, 2021. The complete search strategy is described in the Appendix. In brief, search terms included neoplasm, immune checkpoint inhibitors, and autoimmune disease. The titles and abstracts of the searched articles were screened, and the full text was assessed for eligible studies. Finally, we selected studies that included extractable data for the incidence rate of irAEs in patients with or without PAD. Screening was conducted by two individuals (AY and MK).

### *2.3. Eligibility criteria*

Studies were considered eligible if they were observational studies and reported the number of patients receiving ICIs and the incidence of irAEs with and without PAD. We excluded case reports/case

series, review articles, or studies including the PAD-alone cohort.

#### *2.4. Data extraction*

Data extraction was independently conducted by two authors (AY and MK). We extracted the following data: author, publication year, study design, study period, cancer type, therapeutic agent, characteristics of PAD, and incidence rate of irAEs.

#### *2.5. Data synthesis and statistical analysis*

Data were analyzed using Review Manager 5.4 software (The Cochrane Collaboration, Copenhagen, Denmark) and R (R Foundation for Statistical Computing, Vienna, Austria). Meta-analysis was performed using the fixed effects model and the Mantel-Haenszel (M-H) method. We calculated the odds ratio (OR) and 95% confidence interval (95% CI). Statistical significance was defined as a Z index  $p$ -value  $< 0.05$ . The heterogeneity among studies was assessed using the Cochran Q test ( $\chi^2$ ) and the  $I^2$  statistics:  $\chi^2 p$ -value  $< 0.1$  correlated high heterogeneity;  $I^2 < 25\%$ ,  $25\%–50\%$ , and  $>50\%$  indicated low, moderate, and high heterogeneity, respectively. To explore the possibility of publication bias, we generated funnel plots (visual inspection) and performed Begg's test (rank correlation) and Egger's test (linear regression); an asymmetric funnel plot and a  $p$ -value  $< 0.1$  implied potential publication bias [9, 10].

### **3. Results**

#### *3.1. Study selection and characteristics*

A systematic search of articles identified 600, 552, and 327 reports in MEDLINE/PubMed, Web of Science, and Google Scholar, respectively. After screening these reports, we assessed 32 full-text articles and included 6 articles in this meta-analysis (Figure 1). In total, 206 patients with PAD and 3078 patients without PAD were evaluated. The study characteristics are summarized in Table 1. Among the identified studies, three were retrospective studies [11-13], and the others were prospective studies [14-16]. The incidence of irAEs was the primary endpoint in two studies [12, 13] and secondary in the others [11, 14-16]. In four studies, the patients were mainly treated with an anti-PD-1 antibody (nivolumab, pembrolizumab) [11, 12, 14, 16], and the two remaining studies were based on mixed ICIs (ipilimumab and anti-PD-1 antibody) [13] and atezolizumab [15]. The types of PAD covered a broad range, including rheumatoid arthritis, endocrine disorders, dermatologic disorder, and gastrointestinal disorders. Five studies reported irAEs of any grade [11-13, 15, 16], and one study reported grade 2 or more irAEs [14].

#### *3.2. Quantitative synthesis and meta-analysis*

According to the forest plot of the six studies, the occurrence of all reported irAEs was 62.1% in patients with PAD and 51.9% in non-PAD patients. In addition, the incidence of irAEs was significantly higher in patients with PAD than in non-PAD patients ( $OR = 2.14$ , 95% CI [1.58-2.89],  $Z = 4.94$ ,  $p < 0.05$ )

(Figure 2). The Chi<sup>2</sup> *p*-value was 0.45 and I<sup>2</sup> was 0%, indicating that the heterogeneity was low in this meta-analysis.

### *3.3. Risk of publication bias*

The Begg's test ( $z = 0.19, p = 0.85$ ) and Egger's test ( $t = -0.76, p = 0.49$ ) suggested no publication bias. Although the number of studies was extremely limited to apply funnel plots and data were lacking in the large SE area, visual inspection of the funnel plot might exhibit symmetry (Figure 3).

### *3.4. Subgroup analysis*

Next, we conducted a subgroup analysis of irAEs of any grade for the early detection of irAEs. We eliminated one study that reported grade 2 or more irAEs to unify the outcome and exclude the effects of grade 1 irAEs on our main meta-analysis (Figure 4). The forest plot indicated a similar result as described in all reported irAEs (67.0% in PAD vs. 54.8% in non-PAD; OR = 2.19, 95% CI [1.55-3.08],  $Z = 4.47, p < 0.05$ ). Heterogeneity was also low ( $\text{Chi}^2 = 4.61, p = 0.33, I^2 = 13\%$ ). Based on these results, we suggest that PAD increases the risk of irAEs of any grade.

#### **4. Discussion**

In the present study, we conducted a meta-analysis of six reports to elucidate the influence of ICI therapy on irAEs in patients with PAD. We observed that PAD was significantly associated with a higher risk of irAE incidence ( $OR = 2.14$ ). The incidence of irAEs in the PAD group was 62.1%, which was similar to a previous pooled analysis (60%) that included PAD single-arm observational studies [7]. Therefore, we believe that the population of this study was relevant in evaluating the risk of irAEs. Furthermore, the results of our subgroup analysis were similar to those of the main analysis. The heterogeneity among studies was low, and the integrated effects were significant, suggesting that the results of our meta-analysis could be generalized. Our statistical test (Begg's test and Egger's test) revealed that publication bias was low. In the funnel plot, it was difficult to assess symmetry owing to a lack of data on the base side; therefore, additional studies are needed. In most studies included in our meta-analysis, the patient characteristics were not balanced between PAD and non-PAD patients, except for one study, in which logistic regression analysis (adjusted  $OR = 9.55$ , 95% CI [1.33-68.22],  $p = 0.025$ ) was performed. Accordingly, we unified the incidence of irAEs in patients with or without PAD and estimated crude OR. For this reason, our results might include confounder effects. In addition, 80 of 206 PAD patients (38.8%) had endocrine disorder. Endocrine dysfunction, especially thyroid dysfunction, is one of the most common irAEs and does not preclude further ICI therapy [17]. Consequently, the presence of endocrine disorder in PAD patients may have a confounding effect on the results. Further studies without endocrine PAD patients are required to confirm these points.

In a previous report, Bender *et al.* have researched hospitalization rates, which implied clinically severe cases, in patients with melanoma receiving PD-1 inhibitors and showed that PAD significantly increased the hospitalization rates when compared with non-PAD cases (24.1% vs. 5.8%,  $p < 0.0001$ ) [18]. In another study, PAD was reportedly associated with hospitalization following irAE diagnosis (HR 1.81, 95% CI [1.21-2.71],  $p < 0.05$ ) [19]. These reports support our results and suggest that irAE management in patients with PAD is more challenging than that in non-PAD patients, necessitating additional monitoring of symptoms and statements for appropriate ICI therapy. On the other hand, most patients receiving ICI therapy were admitted to hospital as emergency cases other than irAEs [20, 21]. Considering that the patient with PAD tends to have co-morbidity, we propose to follow up carefully not only irAEs but also exacerbation of co-morbidity in PAD patients. In the present study, the association between PAD and severe irAEs was not evaluated. Thus, further studies, such as a meta-analysis of hospitalization in patients with PAD during ICI treatment, are required.

In clinical settings, an autoimmune disease can develop owing to an increase in autoantibodies such as rheumatoid factor in rheumatoid arthritis, antithyroglobulin antibody, thyroid-stimulating hormone (TSH) receptor antibody in autoimmune thyroid disease, and antinuclear antibody (ANA) in connective tissue disease. Hence, it is considered that preexisting autoantibodies are also associated with irAE incidence and may be valuable clinical biomarkers. Indeed, a study was conducted to assess whether preexisting autoantibodies were associated with the safety and efficacy of ICI treatment in patients with

non-small cell lung cancer and revealed that these preexisting antibodies were associated with irAE incidence, and ICI efficacy was higher in patients with any of the preexisting antibodies [22]. The study also supports our results that PAD increases the risk of irAEs, although autoantibodies do not consistently result in an autoimmune disease. Conversely, ANA was not associated with any grade irAEs, although only a small number of patients were evaluated [23]. The efficacy tended to be superior in patients without ANA, which was not statistically different [23]. Further research is required to elucidate the association between PAD, preexisting autoantibodies, and irAE incidence.

In the present study, Cortellini *et al.* reported that the incidence rate of irAEs of any grade was significantly higher in patients with inactive and active PAD than in those without PAD (64.3%, 73.3%, and 39.9%,  $p = 0.0001$  and  $p = 0.0402$ , respectively) [12]. This rate was similar to that observed in the systematic review of patients with inactive and active PAD (67% and 75%, respectively) [24]. Based on these findings, it can be suggested that the incidence of irAEs is related to PAD, regardless of the baseline autoimmune disease activity.

In general, autoimmune diseases are caused by environmental and genetic factors. The accumulation of these triggers induces the breakdown of immune tolerance and the production of autoreactive B cells, T cells, and autoantibodies, which lead to excessive activation of both innate and adaptive immune cells. Finally, the aberrant immune system induces chronic inflammation and organ-specific or systemic damage [25, 26]. Additionally, autoimmune diseases cause various systemic symptoms.

For example, inflammatory bowel disease presents extraintestinal manifestations such as in the joints, skin, or eyes [27], and rheumatoid arthritis is a risk factor for interstitial lung disease [28], indicating that the immune reactions occur in various tissues in autoimmune diseases, like irAEs. Consequently, we propose a potential mechanism of irAE development in patients with PAD. First, patients with PAD present systemic immune state instability, although clinical symptoms may be absent. The administration of ICIs blocks the immune checkpoint pathways and enhances T-cell effector function. Finally, T-cell activation can easily disrupt the balance of the immune system owing to the fragility of the host immune state, inducing flares of autoimmune disease and systemic irAEs. However, the molecular mechanisms involved, such as regulatory T cells, interleukin (IL), and tumor necrosis factor-alpha (TNF- $\alpha$ ), remain elusive. Further basic research is required to reveal detailed underlying mechanisms.

To avoid irAEs in patients with PAD, immunosuppressive therapy during the early stages may be effective. In the previously discussed systematic review, patients receiving immunosuppressive therapy at the initiation of ICI treatment demonstrated a marginally lower incidence rate of irAEs than those without treatment (67% vs. 74%) [24]. In contrast, baseline corticosteroid use ( $\geq 10$  mg) was associated with worse progression-free survival (hazard ratio, 1.31; 95% CI [1.03-1.67],  $p = 0.03$ ) and overall survival (hazard ratio, 1.66, 95% CI [1.28-2.16],  $p < 0.01$ ) [29]. Therefore, it is necessary to consider corticosteroid administration in patients with PAD depending on symptom severity.

This study has some limitations. First, the number of included reports was small, and four out of

six studies used secondary outcome data. Therefore, the quality of evidence was low, and the evaluation of the funnel plot symmetry might have been insufficient, indicating a potential publication bias. Second, the treatment type (ICI monotherapy or combination with cytotoxic chemotherapy or molecular targeted therapy) was not described in some studies. Third, patient characteristics, such as cancer type, treatment agent, and PAD type, were not unified and balanced in the original studies, and we only estimated crude OR in the meta-analysis. In general, autoimmune diseases are common in women, which may affect the incidence rate of irAEs, although baseline characteristics did not affect irAE incidence [30]. Additionally, we were unable to determine the relationship between these factors and irAEs and to eliminate the confounders. Further studies, taking these adjustments into consideration, are required to definitively conclude that patients with PAD develop irAEs. Fourth, the severity of irAEs was not evaluated. Although the frequency of irAEs and hospitalization rates were increased in patients with PAD, further investigations on severe irAEs are required. Finally, the reported irAEs in patients with PAD might have included PAD flare and *de novo* irAEs, which were not described in detail in the included studies. It is difficult to assess whether the PAD flare could be attributed to ICI treatment. Thus, we might have overestimated irAEs in patients with PAD.

In conclusion, we performed a meta-analysis and identified that PAD is a risk factor for irAE incidence. We believe that this study suggests the importance of carefully monitoring patients with PAD receiving ICIs for early detection with appropriate countermeasures. Accordingly, the establishment of co-

treatments and suitable strategies to promptly collect information regarding patient conditions are required.

**Funding:** (information that explains whether and by whom the research was supported)

None.

**Conflicts of interest/Competing interests:** (include appropriate disclosures)

The authors have no conflicts of interest and competing interests to declare.

**Availability of data and material:** (data transparency)

The dataset used for this study are available from the corresponding author on reasonable request.

**Code availability:** (software application or custom code)

Not applicable.

**Authors contributions :** (include appropriate statements)

AY, YS, and MK designed the study. AY and MK conducted the study and analyzed the data. AY, YS, MK, KO, KN, AF, YT, and MS contributed to the writing of the manuscript. All authors reviewed the results and approved the final version of the manuscript.

**Ethics approval:** (include appropriate approvals or waivers)

Not applicable.

**Consent to participate:** (include appropriate statements)

Not applicable.

**Consent for publication:** (include appropriate statements)

Not applicable.

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### **Figure legends**

Figure 1. Flow diagram of research strategy and study selection.

Figure 2. Forest plot of meta-analysis of all reported immune-related adverse events (irAEs).

Figure 3. Funnel plot of eligible studies.

Figure 4. Forest plot of meta-analysis of any grade irAEs (subgroup analysis).

## **Appendix: search strategy**

We searched the related records in three databases (MEDLINE/PubMed, Web of Science, and Google Scholar), with no language restriction, from database inception to January 31, 2021. In the MEDLINE/PubMed database, we used PubMed Advanced Search Builder with the following terms: (neoplasm) AND (immune checkpoint inhibitors) AND (autoimmune disease) in All Fields. In the Web of Science database, we selected All Databases and conducted a Basic Search with the following terms: (neoplasm) AND (immune checkpoint inhibitors) AND (autoimmune disease) in the Topic field. In Google Scholar, we searched articles using the Advanced Search feature and with the following terms: “neoplasm” AND “immune checkpoint inhibitors” AND “autoimmune disease”, with all of the words appearing anywhere in the article. Default values were chosen for all other settings.

Table.1 Characteristics of the eligible studies

<b>Study</b>	<b>Study design and period</b>	<b>Cancer type</b>	<b>Therapeutic agent</b>	<b>Characteristics of PAD</b>	<b>irAEs grade</b>
<b>Bair</b>	Retrospective	R/R cHL	Anti PD-1 antibody	Lupus (n = 1)	Any grade irAEs
<b>2019 [11]</b>	Jan 2014 – Nov 2017		Nivolumab (n = 52)	Inflammatory bowel disease (n = 1)	
			Pembrolizumab (n = 1)	Psoriasis (n = 1)	
				Unknown (n = 1)	
<b>Cortellini</b>	Retrospective	Advanced cancer (stage IV)	Anti PD-1 antibody	Thyroid disorders (n = 51)	Any grade irAEs
<b>2019 [12]</b>	Sep 2013 – May 2018	NSCLC (n = 492)	Pembrolizumab (n = 182)	Dermatologic (n = 14)	
		Melanoma (n = 159)	Nivolumab (n = 569)	Rheumatologic (n = 10)	
		RCC ( n = 94)		Gastrointestinal/hepatic (n = 4)	
		Others (n = 6)		Neurologic (n = 1)	
				Nephrologic (n = 1)	
				Multiple site (n = 4)	
<b>Danlos</b>	Prospective	Melanoma (n = 36)	Pembrolizumab (n = 34)	Rheumatic (n = 7)	≥ Grade 2 irAEs
<b>2018 [14]</b>	Jun 2014 – Dec 2016	NSCLC (n = 6)	Nivolumab (n = 10)	Dermatologic (n = 33)	
		Other cancers (n = 3)	Avelumab (n = 1)	Endocrine (n = 9)	
		(Only PAD cohort was described)	(Only PAD cohort was described)	Neurologic (n = 3)	
				Haematologic (n = 1)	

<b>Kartolo</b>	Retrospective	Melanoma (n = 55)	Ipilimumab (n = 25)	Unknown	Any grade irAEs
<b>2018 [13]</b>	Jan 2012 – Apr 2017	NSCLC (n = 17)	Pembrolizumab (n = 27)		
		RCC (n = 6)	Nivolumab (n = 26)		
<b>Loriot</b>	Prospective	Locally advanced/metastatic urothelial carcinoma or nonurothelial carcinoma (n = 997)	Atezolizumab (n = 997)	Psoriasis (n = 15) Rheumatoid arthritis (n = 4) Hypothyroidism or Thyroiditis (n = 4) Ulcerative colitis (n = 2) Hashimoto's disease (n = 2) Sarcoidosis (n = 2) Graves disease (n = 2) Others (n = 4)	Any grade irAEs
<b>2020 [15]</b>	Nov 2016 – Mar 2018				
<b>Schadendorf</b>	Prospective	stage III or IV melanoma (n = 1008)	Nivolumab (n = 1008)	Endocrine (n = 14) Gastrointestinal (n = 2) Hepatic (n = 1) Skin (n = 7) Other (n = 1)	Any grade irAEs
<b>2019 [16]</b>	Aug 2017 – Jan 2019				

Abbreviations: R/R cHL, relapsed/refractory classical Hodgkin lymphoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; PAD, pre-existing autoimmune disease.

**Identification / Screening**

Records identified through  
MEDLINE/PubMed  
(n = 600)

Records identified through  
Web of Science  
(n = 552)

Records identified through  
Google Scholar  
(n = 327)

Studies excluded after reading  
titles and abstracts  
(n = 586)

Studies excluded after reading  
titles and abstracts  
(n = 539)

Studies excluded after reading  
titles and abstracts  
(n = 322)

Full-text articles  
assessed for eligibility  
(n = 14)

Full-text articles  
assessed for eligibility  
(n = 13)

Full-text articles  
assessed for eligibility  
(n = 5)

**Eligibility**

Candidate studies  
(n = 32)

Excluding articles  
duplication (n = 8)  
No extractable data (n = 18)

**Included**

Studies included in meta-analysis  
(n = 6)





