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ORIGINAL ARTICLE

S100A12 Protein Levels in Juvenile Idiopathic Arthritis (JIA): a Systematic Review and Meta-Analysis

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SUMMARY

Background: **Juvenile idiopathic arthritis (JIA) is a childhood inflammatory disease, which is a common cause of disability among the younger population. S100A12 protein level is found to be associated with the patients of JIA; though, the findings on this are inconsistent. Therefore, we conducted a systematic review and meta-analysis to assess the association of S100A12 protein levels with juvenile idiopathic arthritis.**

Methods: **Relevant published studies up to December 2022 were identified by systematic literature searching on Embase, PubMed/Medline, Web of Science, and Scopus for exploring the association of S100A12 protein levels with juvenile idiopathic arthritis (JIA). The data analysis was performed using the R-4.4.0 software.**

Results: **We included 9 eligible studies on serum S100A12 protein levels in JIA and healthy controls, which encompassed 518 JIA patients and 345 healthy control subjects. The pooled analysis revealed that the serum S100A12 protein levels increased significantly (summary SMD = 2.18, 95% CI: 0.63 - 3.74, overall effect size z = 2.76, $p < 0.01$) in JIA subjects in comparison to healthy control subjects. The pooled results of subgroup analysis for the Europe and Asia group' studies were SMD = 2.75, (95% CI [-0.09 to 5.58]; $p < 0.01$) and SMD = 1.53, (95% CI [-0.27 to 3.32]; $p < 0.01$), respectively, and both groups based on geographical regions exhibited significant heterogeneity ($I^2 = 97.0\%$ and $I^2 = 98.0\%$ respectively, $p < 0.01$). Similarly, in cohort and case-control study groups, the results were SMD = 1.70, (95% CI [0.36 to 3.04]; $p < 0.01$) and SMD = 1.29, (95% CI [0.03 to 2.55]; $p < 0.01$), respectively, and both groups based on study type also exhibited significant heterogeneity ($I^2 = 97.0\%$ and $I^2 = 96.0\%$, respectively, $p < 0.01$).**

Conclusions: **This meta-analysis suggests that the S100A12 protein serum concentrations of JIA were significantly higher than those of healthy controls, which suggests that serum S100A12 protein could be a potential biomarker for JIA.**

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Supplementary Data

Table S1. Studies excluded during full-text evaluation.

Study ID	Criteria of exclusion	Reference
Gohar et al. 2018	Scientific abstract	Gohar F, McArdle A, Jones M, et al. Proteomic identification of systemic-onset juvenile idiopathic arthritis phenotypic biomarkers. Ann Rheum Dis 2018;77(Suppl 2):487. https://www.embase.com/search/results?subaction=viewrecord&id=L623992543&from=export
Kessel et al. 2017	Conference abstract	Kessel C, Fuehner S, Zimmermann B, et al. An extracellular ionic milieu renders human granulocytic S100A12 into a pro-inflammatory TLR4-binding alarmin [abstract]. Arthritis Rheumatol 2017;69(4):48-9. https://acrabstracts.org/abstract/an-extracellular-ionic-milieu-renders-human-granulocytic-s100a12-into-a-pro-inflammatory-tlr4-binding-alarmin/
Lundestad et al. 2021	Conference abstract	Lundestad A, Cetrelli LE, Frid P, et al. Biomarkers in juvenile idiopathic arthritis associated with inflammation and bone health. Pediatr Rheumatol 2021;19:suppl 1. https://www.embase.com/search/results?subaction=viewrecord&id=L636613508&from=export
Ter Haar et al. 2017	Conference abstract	Ter Haar N, Scholman R, De Jager W, et al. Biomarkers in systemic onset juvenile idiopathic arthritis: Prediction of therapy response. Pediatr Rheumatol 2017;15(Suppl 1). https://www.embase.com/search/results?subaction=viewrecord&id=L618532849&from=export
Hinze et al. 2022	Conference abstract	Hinze C, Saers M, Kessel C, et al. Comparative analysis of serum biomarkers and peripheral blood gene expression in systemic juvenile idiopathic arthritis and macrophage activation syndrome. Pediatr Rheumatol 2022;20(Suppl 2). https://www.embase.com/search/results?subaction=viewrecord&id=L639228694&from=export
Klotsche et al. 2022	Conference abstract	Klotsche J, Sengler C, Dressler F, et al. Course of uveitis in children with juvenile idiopathic arthritis: data from the Inception Cohort of Newly diagnosed patients with JIA (ICON-JIA) study. Ann Rheum Dis 2022;81:420-1. https://www.embase.com/search/results?subaction=viewrecord&id=L638908842&from=export
Turnier et al. 2015	Conference abstract	Turnier J, Fall N, Grom AA, Thornton S, Brunner HI. Highly Elevated S100A8/A9 and S100A12 Levels May Distinguish Systemic Juvenile Idiopathic Arthritis Patients with New Onset Disease and Subclinical Macrophage Activation Syndrome [abstract]. Arthritis Rheumatol 2015;67(Suppl 10). https://acrabstracts.org/abstract/highly-elevated-s100a8a9-and-s100a12-levels-may-distinguish-systemic-juvenile-idiopathic-arthritis-patients-with-new-onset-disease-and-subclinical-macrophage-activation-syndrome/
Orczyk et al. 2018	Conference abstract	Orczyk K, Smolewska E. Personalised treatment in juvenile idiopathic arthritis– future or fiction? preliminary results of using s100a8a9, s100a12 and vascular endothelial cadherin as diagnostic and prognostic biomarkers. EULAR Annual Congress 2018;493. https://www.embase.com/search/results?subaction=viewrecord&id=L623991363&from=export
Walscheid et al. 2017	Conference abstract	Walscheid K, Tappeiner C, Klotsche J, et al. Risk for uveitis occurrence in juvenile idiopathic arthritis (JIA) and predictive factors for the 2-years outcome: Data from the Inception Cohort of Newly diagnosed patients with JIA (ICON-JIA) study. Invest Ophthalmol Vis Sci 2017;58(8):2157. https://www.embase.com/search/results?subaction=viewrecord&id=L621489534&from=export
Holzinger et al. 2015	Conference abstract	Holzinger D, Fall N, Grom A, et al. S100A12 as diagnostic tool in the differential diagnosis of sJIA associated MAS vs. hereditary or acquired HLH. Pediatr Rheumatol 2015;13:(Suppl 1):O64. https://www.embase.com/search/results?subaction=viewrecord&id=L607880009&from=export

Table S1. Studies excluded during full-text evaluation (continued).

Study ID	Criteria of exclusion	Reference
Malul et al. 2012	Conference abstract	Malul G, Whitbred JM, O'Riordan M, et al. S100A12 at baseline may be useful for predicting inactive disease within 12 months in Polyarticular Juvenile Idiopathic Arthritis. Arthritis Rheumatol 2012;64(10):S1098-9. https://acrabstracts.org/abstract/s100a12-at-baseline-may-be-useful-for-predicting-inactive-disease-within-12-months-in-polyarticular-juvenile-idiopathic-arthritis/
Ruperto N et al. 2021	Conference abstract	Ruperto N, Schulert G, Sproles A, et al. S100A8/A9 and S100A12 as potential predictive biomarkers of abatacept response in polyarticular juvenile idiopathic arthritis. Ann Rheum Dis 2021;80(1):245-6. https://www.embase.com/search/results?subaction=viewrecord&id=L635708847&from=export
Lovell et al. 2017	Conference abstract	Lovell DJ, Ringold S, Eastman PS. Validation of Biomarkers to Predict Flare in Polyarticular JIA upon Stopping Anti-TNF Therapy. Arthritis Rheumatol 2017;69(10). https://www.embase.com/search/results?subaction=viewrecord&id=L618916785&from=export
Kessel et al. 2021	Irrelevant study	Kessel C, Fall N, Grom A, et al. Definition and validation of serum biomarkers for optimal differentiation of hyperferritinaemic cytokine storm conditions in children: a retrospective cohort study. Lancet Rheumatol 2021;3(8):e563-73. (PMID: 38287622)
Cai et al. 2016	Irrelevant study	Cai J, Han T, Nie C, et al. Biomarkers of oxidation stress, inflammation, necrosis and apoptosis are associated with hepatitis B-related acute-on-chronic liver failure. Clin Res Hepatol Gastroenterol 2016;40(1):41-50. (PMID: 26189982)
Cai et al. 2021	Irrelevant study	Cai L, Zhang C, Wu J, Zhou W, Chen T. Unbalanced expression of membrane-bound and soluble programmed cell death 1 and programmed cell death ligand 1 in systemic juvenile idiopathic arthritis. Clin Immunol 2021;229:108800. (PMID: 34289424)
Angeles-Han et al. 2021	Irrelevant study	Angeles-Han ST, Utz VM, Thornton S, et al. S100 proteins, cytokines, and chemokines as tear biomarkers in children with juvenile idiopathic arthritis-associated uveitis. Ocul Immunol Inflamm 2021;29(7-8):1616-20. (PMID: 35169380)
Kessel et al. 2018	Letter to the editor	Kessel C, Fuehner S, Zell J, et al. Calcium and zinc tune autoinflammatory Toll-like receptor 4 signaling by S100A12. J Allergy Clin Immunol 2018;142(4):1370-3. (PMID: 30010542)
Walscheid et al. 2015	Relevant data not available	Walscheid K, Heiligenhaus A, Holzinger D, et al. Elevated S100A8/A9 and S100A12 serum levels reflect intraocular inflammation in juvenile idiopathic arthritis-associated uveitis: results from a pilot study. Invest Ophthalmol Vis Sci 2015;56(13):7653-60. (PMID: 26624497)
Rodriguez-Smith et al. 2021	Relevant data not available	Rodriguez-Smith JJ, Verweyen EL, Clay GM, et al. Inflammatory biomarkers in COVID-19-associated multisystem inflammatory syndrome in children, Kawasaki disease, and macrophage activation syndrome: a cohort study. Lancet Rheumatol 2021;3(8):e574-84. (PMID: 34124694)
Hinze et al. 2021	Relevant data not available	Hinze T, Kessel C, Hinze CH, Seibert J, Gram H, Foell D. A dysregulated interleukin-18-interferon-γ-CXCL9 axis impacts treatment response to canakinumab in systemic juvenile idiopathic arthritis. Rheumatology (Oxford) 2021;60(11):5165-74. (PMID: 33576397).
Yamasaki et al. 2019	Relevant data not available	Yamasaki Y, Takei S, Imanaka H, et al. S100A12 and vascular endothelial growth factor can differentiate Blau syndrome and familial Mediterranean fever from systemic juvenile idiopathic arthritis. Clin Rheumatol 2019;38(3):835-40. (PMID: 30406853)
Gohar et al. 2018	Relevant data not available	Gohar F, Anink J, Moncrieffe H, et al. S100A12 is associated with response to therapy in juvenile idiopathic arthritis. J Rheumatol 2018;45(4):547-54. (PMID: 29335345)
Hinze et al. 2019	Relevant data not available	Hinze CH, Foell D, Johnson AL, et al. Serum S100A8/A9 and S100A12 levels in children with polyarticular forms of juvenile idiopathic arthritis: relationship to maintenance of clinically inactive disease during anti-tumor necrosis factor therapy and occurrence of disease flare after discontinuation of therapy. Arthritis Rheumatol 2019;71(3):451-9. (PMID: 30225949)

Table S1. Studies excluded during full-text evaluation (continued).

Study ID	Criteria of exclusion	Reference
Ward et al. 2016	Relevant data not available	Ward TM, Yuwen W, Voss J, Foell D, Gohar F, Ringold S. Sleep fragmentation and biomarkers in juvenile idiopathic arthritis. Biol Res Nurs 2016;18(3):299-306. (PMID: 26512051)
Kessel et al. 2022	Relevant data not available	Kessel C, Koné-Paut I, Tellier S, et al. An Immunological Axis Involving Interleukin 1β and Leucine-Rich-α2-Glycoprotein Reflects Therapeutic Response of Children with Kawasaki Disease: Implications from the KAWAKINRA Trial. J Clin Immunol 2022;42(6):1330-41. (PMID: 35699824)
Schierbeck et al. 2013	Relevant data not available	Schierbeck H, Pullerits R, Pruunsild C, et al. HMGB1 levels are increased in patients with juvenile idiopathic arthritis, correlate with early onset of disease, and are independent of disease duration. J Rheumatol 2013;40(9):1604-13. (PMID: 23858044)
Qu et al. 2021	Relevant data not available	Qu H, Sundberg E, Aulin C, et al. Immunoprofiling of active and inactive systemic juvenile idiopathic arthritis reveals distinct biomarkers: a single-center study. Pediatr Rheumatol Online J 2021;19(1):173. (PMID: 34963488)
Gerss et al. 2022	Relevant data not available	Gerss J, Tedy M, Klein A, et al. Prevention of disease flares by risk-adapted stratification of therapy withdrawal in juvenile idiopathic arthritis: results from the PREVENT-JIA trial. Ann Rheum Dis 2022;81(7):990-7. (PMID: 35260388)
Tappeiner et al. 2018	Relevant data not available	Tappeiner C, Klotsche J, Sengler C, et al. Risk factors and biomarkers for the occurrence of uveitis in juvenile idiopathic arthritis: data from the inception cohort of newly diagnosed patients with juvenile idiopathic arthritis study. Arthritis Rheumatol 2018;70(10):1685-94. (PMID: 29732713)
Madland et al. 2007	Relevant data not available	Madland TM, Larsen A, Brun JG. S100 proteins calprotectin and S100A12 are related to radiographic changes rather than disease activity in psoriatic arthritis with low disease activity. J Rheumatol 2007;34(10):2089-92. (PMID: 17787039)
Routhmund et al. 2014	Relevant data not available	Rothmund F, Gerss J, Ruperto N, et al. Validation of relapse risk biomarkers for routine use in patients with juvenile idiopathic arthritis. Arthrit Care Res (Hoboken) 2014;66(6):949-55. (PMID: 24339418)
Ganeva et al. 2021	Relevant data not extracted	Ganeva M, Fuehner S, Kessel C, et al. Trajectories of disease courses in the inception cohort of newly diagnosed patients with JIA (ICON-JIA): the potential of serum biomarkers at baseline. Pediatr Rheumatol Online J 2021;19(1):64. (PMID: 33933108)
Brown et al. 2018	Relevant data not extracted	Brown RA, Grom AA, Schulert GS. Neutrophils from children with systemic juvenile idiopathic arthritis exhibit persistent proinflammatory activation despite long-standing clinically inactive disease. Front Immunol 2018;9:2995. (PMID: 30619348)
Holzinger et al. 2018	Review paper	Holzinger D, Tenbrock K, Roth J. Alarmins of the S100-family in juvenile autoimmune and auto-inflammatory diseases. Front Immunol 2019;10:182. (PMID: 30828327)

Table S2. Risk of bias assessments according to the Joanna Briggs Institute´s critical appraisal checklist.

Cohort studies											
Studies	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**
Wittkowski et al. 2008	yes	yes	yes	yes	yes	unclear	yes	yes	unclear	unclear	yes
Wittkowski et al. 2007	yes	yes	yes	unclear	unclear	unclear	yes	yes	unclear	unclear	yes
Foell et al., 2004	yes	yes	yes	yes	yes	unclear	yes	yes	yes	unclear	yes
Myles et al., 2011	yes	yes	yes	unclear	unclear	unclear	yes	yes	yes	unclear	yes
Questions (Q): **Q1: Were the two groups similar and recruited from the same population?** **Q2: Were the exposures measured similarly to assign people to both exposed and unexposed groups?** **Q3: Was the exposure measured in a valid and reliable way?** **Q4: Were confounding factors identified?** **Q5: Were strategies to deal with confounding factors stated?** **Q6: Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?** **Q7: Were the outcomes measured in a valid and reliable way?** **Q8: Was the follow-up time reported and sufficient/long enough for outcomes to occur?** **Q9: Was follow up complete, and if not, were the reasons for loss to follow up described and explored?** **Q10: Were strategies to address incomplete follow up utilized?** **Q11: Was appropriate statistical analysis used?**										

Case control studies										
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**
Orczyk et al., 2018	yes	yes	yes	yes	yes	yes	unclear	yes	yes	yes
Al Bassam et al., 2020	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Abdul-Aziez et al., 2010	yes	yes	yes	yes	yes	yes	unclear	yes	yes	yes
Dumur et al., 2023	no	no	unclear	yes	yes	unclear	unclear	yes	unclear	yes
Questions (Q): **Q1: Were the groups comparable, other than in the presence of disease in cases or the absence of disease in controls?** **Q2: Were cases and controls matched appropriately?** **Q3: Were the same criteria used for identification of cases and controls?** **Q4: Was exposure measured in a standard, valid, and reliable way?** **Q5: Was exposure measured in the same way for cases and controls?** **Q6: Were confounding factors identified?** **Q7: Were strategies to deal with confounding factors stated?** **Q8: Were outcomes assessed in a standard, valid, and reliable way for cases and controls?** **Q9: Was the exposure period of interest long enough to be meaningful?** **Q10: Was appropriate statistical analysis used?**									

Cross-sectional study								
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**
Bobek et al., 2023	yes	yes	yes	yes	no	no	yes	yes
Questions (Q): **Q1: Were the criteria for inclusion in the sample clearly defined?** **Q2: Were the study subjects and the setting described in detail?** **Q3: Was the exposure measured in a valid and reliable way?** **Q4: Were objective standard criteria used for measurement of the condition?** **Q5: Were confounding factors identified?** **Q6: Were strategies to deal with confounding factors stated?** **Q7: Were the outcomes measured in a valid and reliable way?** **Q8: Was appropriate statistical analysis used?**								

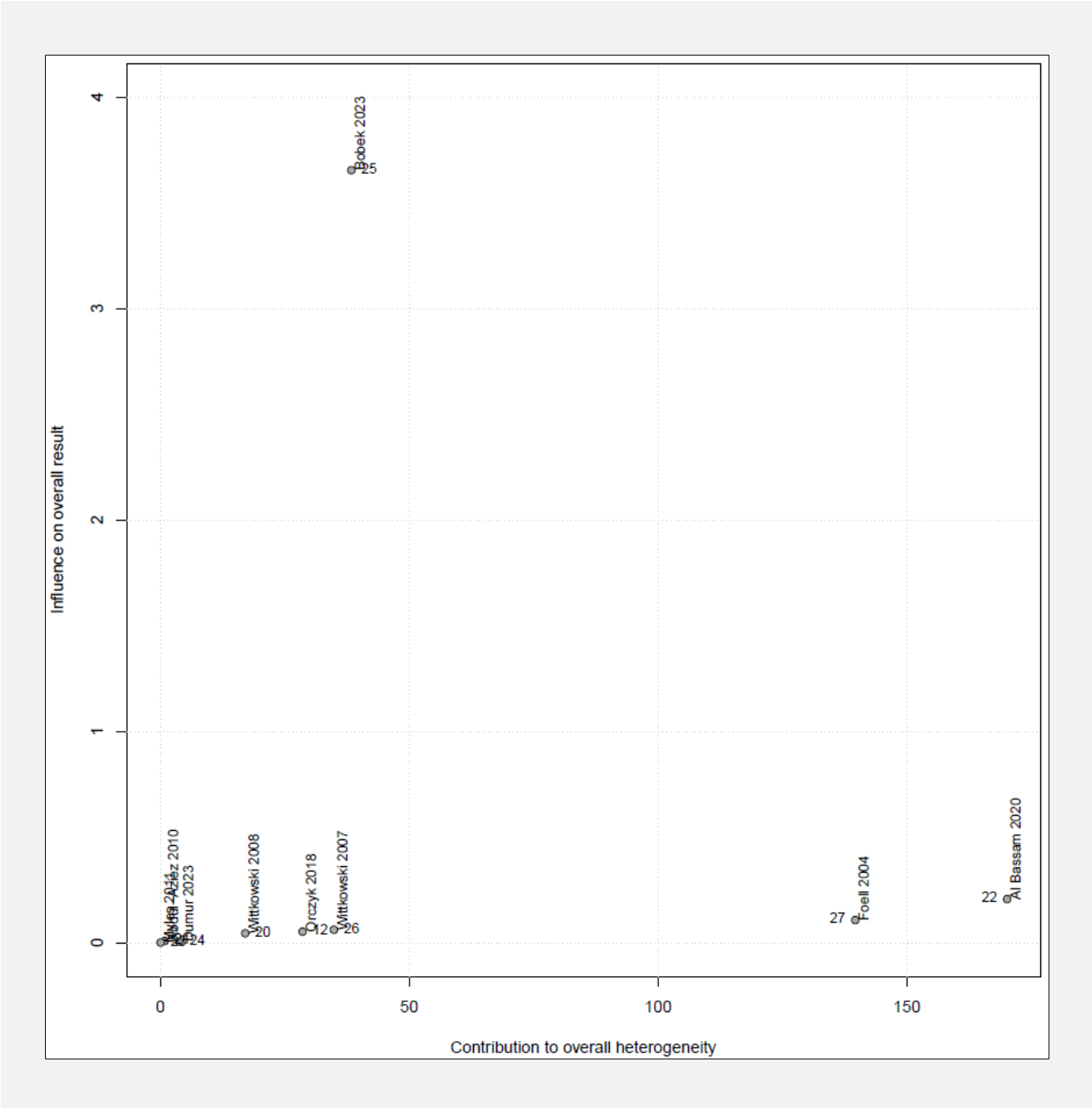

Figure S1. Baujat plot identifying studies which contributed maximal to the heterogeneity.