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Environmental determinants of juvenile idiopathic arthritis: current evidence and future directions

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ABSTRACT

The hypothesis that environmental factors may contribute to the development of juvenile idiopathic arthritis (JIA) arises from the variability observed in the incidence of its various subtypes across different geographic regions and ethnic groups. However, despite decades of research, the evidence of most associations remains weak and subject to confounding factors. In recent years, a number of environmental factors have been investigated for a possible role in the development of JIA, as risk factors or protective agents. As a result, the most plausible pathogenic pathway involves early-life gut microbiota disruption, particularly in relation to early antibiotic exposure. Prenatal factors such as maternal diet and weight gain, and smoking and pollutant exposures during pregnancy require further clarification and should be interpreted with caution given the limitations of existing data. Other associations with perinatal events, such as breastfeeding and caesarean section delivery, living or socioeconomic conditions, and infections, remain suggestive but not definitive. Furthermore, the complexity of JIA as a heterogeneous group of diseases underscores the difficulty of identifying universal environmental drivers. In order to better define the role of environmental factors in JIA development, there is a need for a shift from retrospective, population-based studies to an integrated and longitudinal research approach. This step requires international, harmonized datasets and collaborative consortia, possibly employing existing international networks. Until robust evidence emerges, the current knowledge should be interpreted cautiously, avoiding oversimplified or causal claims.

1. Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood, with an estimated incidence varying from 1.6 to 23/100,000/year and an estimated prevalence ranging from 3.8 to 400/100,000.[1–3] It is widely accepted that JIA is not a single disease, as under this umbrella term are grouped at least five different subtypes of chronic arthritides of unknown origin with onset before the age of 16.[3,4] The current classification criteria were developed >20 years ago by the International League of Associations for Rheumatology and comprise oligoarticular JIA, (rheumatoid factor positive and negative) polyarticular JIA, systemic JIA/Still's disease, psoriatic arthritis, and enthesitis-related arthritis (ERA); forms fulfilling criteria for more forms or not fulfilling any criteria for a specific subtype are categorized as undifferentiated JIA.[4,5] Over the past years, a growing need for a more accurate and specific classification system emerged, and a revision process has been initiated by the Paediatric Rheumatology INternational Trials Organization (PRINTO).[6]

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Notably, JIA is more common in females than males (estimated incidence of 10 vs. 5.7/100,000/year, estimated prevalence ratio of 6.6–3:1), and there is a substantial variability in the prevalence of the different JIA subtypes across diverse world regions.[2,7,8] For instance, oligoarticular JIA is the most common form in individuals of European ancestry, polyarticular JIA is most often observed in non-White cohorts, ERA is more common in southeastern Asia, and systemic JIA/Still's disease is more commonly observed in Africa, Asia, Latin America, and the Middle East.[4,6,9–11] In this context, environmental factors appear to play a relevant role in both the development and progression of the disease.[12–16] The aim of this narrative review is to summarize the current state of knowledge in the field and outline future directions to better characterize the impact of environmental determinants on JIA. To this end, relevant medical literature from the past 30 years has been reviewed, including narrative and systematic reviews and research articles.

2. Parental and prenatal factors

In recent years, there has been interest in possible associations between parental and prenatal factors and JIA. Firstly, according to a recent systematic review and meta-analysis, there is no evidence that maternal or paternal age has a role in the development of the disease.[13,17] Conversely, a protective effect was found for maternal multiparity but with uncertain estimates.[13,18] Single studies reported an increased risk of developing JIA for children of mothers with fertility issues[19] or with maternal lower cutaneous sun exposure, with a dose-dependent effect.[20] The presence of (any) siblings and maternal prenatal smoking seem to have a protective effect on JIA development later in life.[13,18,21,22] However, most of the evidence for a protective role for prenatal smoking in JIA arises from a single case-control study where the authors could not rule out the potential effect of confounding such as socioeconomic status.[21] Furthermore, a subsequent study conducted by the same study group did not find any association between JIA and household or maternal prenatal smoking[23], while different authors found an increased risk for intrauterine cigarette smoke exposure.[24] Birth order and sibling number do not seem to have a consistent association with the development of JIA.[13] According to a population-based prospective birth cohort of >15,000 children, consuming fish more than once a week during pregnancy could be linked to an increased risk of JIA, possibly due to exposure to heavy metals in the diet.[25] Interestingly, more recent research found a modestly increased risk of JIA associated with high maternal intake of lean/semi-oily fish during pregnancy even though this association was not explained by estimated exposure to dietary contaminants.[26] Some authors reported that prenatal exposure to air pollution (sulfur dioxide) may represent a risk factor for JIA development.[24] The role of antibiotics during pregnancy has been largely investigated; however, according to the latest evidence, there is no association between prenatal antibiotic exposure and JIA (Table 1).[27]

3. Perinatal factors

A number of perinatal environmental factors have been linked to JIA in the literature. Among them, the strongest association is with caesarean section delivery.[17] According to a recent systematic review and meta-analysis, there is a slightly increased risk for caesarean versus vaginal delivery.[13] However, among the three studies included in the meta-analysis, only the one with the greatest weight was statistically

Table 1
Environmental factors associated with juvenile idiopathic arthritis.

Environmental factors	Possible association	Evidence level	Interpretation
Parental and prenatal factors			
Maternal multiparity	Protective effect	Single studies[18,22,42]	Imprecise estimates
Prenatal smoking	Protective effect (counterintuitive)	Meta-analyses (pooled OR 0.70, 95% CI: 0.58, 0.84)[13]	Most of the pooled analysis based on a single study (weight 85%) with likely socioeconomic confounding[21], opposite results from a subsequent study from same authors[23]
High fish/lean or semi-oily fish intake during pregnancy	Increased risk	Population-based cohorts[25,26]	Mechanisms unclear, not fully explained by contaminants (heavy metals)
Maternal fertility problems	Increased risk	Single study[19]	Possible confounders
Maternal lower sun exposure (dose-dependent effect)	Increased risk	Single study[20]	Possible confounders
Prenatal SO_2 exposure	Increased risk	Single study[24]	Possible confounders
Perinatal factors			
Cesarean delivery	Increased risk	Meta-analyses (pooled OR 1.11, 95% CI: 1.01, 1.22)[13]	Most of the pooled analysis based on a single study (weight 59.1%).[17] Mechanisms likely related to disrupted neonatal microbiota acquisition
Elective vs emergency cesarean	Increased risk	Single study[28]	Possible confounders
Low Apgar score (<6)	Protective effect	Single study[17]	Possible confounders
Ideal maternal weight gain during pregnancy	Protective effect	Single study[24]	Possible confounders
Early-life factors			
Early antibiotic exposure	Increased risk (dose-dependent effect suggested by some authors)	Multiple studies[27,35–39]	Possible confounders such as infections. Mechanisms likely related to long-lasting influence on the composition and diversity of the gut microbiota
Early fish consumption	Increased risk	Single study[25]	Mechanisms unclear, not fully explained by contaminants (heavy metals)
Socioeconomic and living factors			
Higher socioeconomic level	Increased risk	Single study[42]	Mechanisms may reflect hygiene hypothesis; findings not consistently replicated
Urban living	Increased risk	Single study[32]	Mechanisms may reflect hygiene hypothesis; findings not consistently replicated
Moderate air pollutant (ozone) exposure	Increased risk	Single study[24]	Possible confounding, no dose-dependent gradient
Other factors			
Infections	Increased risk	Multiple studies[13,17,44–47]	No specific pathogen definitively implicated, analyses often unadjusted for confounding
Having any siblings	Protective effect	Meta-analyses (pooled OR 0.6, 95% CI: 0.44, 0.81)[13]	Overall effect uncertain; likely confounded by socioeconomic status, birth order, household microbial exposure

significant, and confounding factors may have influenced the results.[13,17,18,23] Some authors highlighted a role for elective caesarean delivery alone, with no evidence for acute caesarean delivery.[28] Despite single studies reporting a possible increased risk for children born pre-term[23] or with high birth weight[17], and a reduced risk for children born pre-term[17] or with low birth weight[29], there is no evidence from the pooled analysis that delivery timing (pre- or post-term) and birth weight (absolute and relative to gestational age) are associated with JIA development.[13] Little evidence from single studies has been reported for a possible protective effect for low Apgar score[17], ideal maternal weight gain[24], and specific birth months[30]; however, subsequent reports did not find any association between JIA and birth season.[13]

4. Early life factors

The role of breastfeeding has been largely investigated for a possible association with JIA development. However, there is no evidence that breastfeeding duration and status may have a role in the process (protective effect), and only single case-control studies[31] have found significant results, but these data were not confirmed by subsequent reports.[13,23,32,33] A different study group reported that a longer duration of breastfeeding may protect against JIA development[34] but, again, these findings have not been confirmed by other reports.[13,23,32] Similar to pregnancy, also consuming fish more than once a week during a child's first year has been found to have an increased risk of developing antinuclear antibody positivity and JIA.[13,25]

Early-life antibiotic exposure has extensively been studied for a possible association with the development of JIA.[27,35–39] Indeed, the use of systemic antibiotics during the first months of life may cause a long-lasting influence on the composition and diversity of the gut microbiota in children, with unexpected long-term effects.[40,41] According to a large case-control study conducted in a wide population-representative medical records database from the United Kingdom, antibiotics were associated with newly diagnosed JIA in a dose- and time-dependent manner, and the relationship was strongest for exposures within 1 year of diagnosis.[39] Similar results were found from different authors conducting a large national case-control study in Finland, especially for lincosamides and cephalosporins and in the overall exposure to antibiotics before 2 years of age.[38] A dose-dependent effect was also confirmed by subsequent studies, as well as a stronger risk for broad-spectrum antibiotics and sulfonamides/trimethoprim.[27,37] In a subsequent study, a direct analysis of stool samples from JIA patients highlighted a higher abundance of Acidaminococcales, Prevotella 9, and Veillonella parvula than controls, and a lower abundance of Coprococcus, Subdoligranulum, Phascolarctobacterium, Dialister spp., Bifidobacterium breve, Fusicatenibacter saccharivorans, Roseburia intestinalis, and Akkermansia muciniphila.[35] Increased antibiotic exposure and shorter breastfeeding duration may compound risk in a dose-dependent manner.[35]

5. Socioeconomic and living factors

Living and socioeconomic factors may have a role in JIA development. However, these factors have been investigated by a relatively low number of studies, and the results that have emerged are not based on robust evidence.[13] As an example, only single studies reported an association (increased risk) between JIA development and higher maternal education[32] and higher household income.[42] Furthermore, according to one of these studies, children living in an urban flat may have a higher risk of developing JIA than children living on a farm.[42] However, again, these associations have not been confirmed by additional reports focusing on early life contact with animals or residential area data from other studies.[13,23,29] As an air pollutant, exposure to moderate levels of ozone (2nd tertile in the study, 80.8–87.1 μg/m^3) during the second year of life has been advocated as a significant risk factor for the pathogenesis of JIA.[24] Nevertheless, in this study there was no evidence of an association between exposure to higher levels of ozone (3rd tertile in the study, >87.1 μg/m^3) and JIA (overall and regarding different subtypes), raising doubts on the role of confounding factors.[24] Some authors highlighted how climate change and extreme heat have also increased the rate of allergic diseases in children[43]; this phenomena might also play a role in pediatric autoimmune diseases, including JIA.

6. Other factors

Infectious agents have long been suspected as triggers, but no specific pathogen has been definitively implicated, as most data come from unadjusted analyses and evidence arises from single research studies.[12,13] According to a large register-based case-control study, infections during the first year of life increase the risks for JIA and seronegative rheumatoid arthritis.[17] Other studies highlighted a possible role in JIA for upper respiratory tract infections,[44] mycoplasma pneumoniae,[45] and parvovirus B19.[46,47] Nevertheless, additional research did not confirm these data, and the role of such infections has not been fully elucidated.[13] Lastly, a recent study evaluating the role of faecal microbiome in new-onset JIA patients did not find any significant difference in stool samples from healthy controls.[48]

7. Environmental factors associated to JIA: a balanced viewpoint

The hypothesis that environmental factors may contribute to the development of JIA arises from the variability observed in the incidence of its various subtypes across different geographic regions and ethnic groups. Moreover, as in most autoimmune diseases, females are more frequently affected than males, probably reflecting intrinsic epigenetic mechanisms. The available evidence suggests that environmental factors may influence disease susceptibility through effects on immune maturation, microbiota composition, and epigenetic regulation. However, although decades of research, the strength of most associations remains weak and subject to confounding factors. Studies evaluating maternal sun exposure, pollution, and dietary habits during pregnancy provide suggestive but inconclusive associations. Similarly, some associations between prenatal maternal smoking and a reduced risk of JIA development appear somehow statistically significant but biologically counterintuitive and likely confounded by socioeconomic or behavioural factors. In a similar manner, high maternal consumption of some fish species during pregnancy has been linked to an increased risk of JIA, initially attributed to heavy metal exposure, though later studies indicate that the mechanism may be more complex and not fully explained. Perinatal exposures should be discussed with special attention due to their possible influence on immune and microbiota development. The reported association between JIA and caesarean section delivery may be explained with a disrupted neonatal microbiota acquisition, as these children are not delivered through the birth canal. However, the effect size is small, and most studies are not able to separate the influence of surgical indication with maternal comorbidities. Despite encouraging results arise from single studies, birth timing and weight do not demonstrate consistent associations with JIA when evaluated in pooled analyses. Early-life factors provide one of the most biologically plausible pathways linking the environment with immune-mediated diseases. Among these, antibiotic exposure in infancy is the most consistently reported factor, with observational evidence of a dose-dependent association and stronger effects for broad-spectrum agents. These findings may be explained with the fact that early disruption of the gut microbiota may have lasting long-term effects on immune regulation. However, again, the interpretation of such results is not easy as antibiotic use is also an indicator of underlying infection, and infections themselves may influence immune development and adaptation. Infectious triggers are themselves under investigation for a possible role in JIA development, but most of these associations are based on small or unadjusted studies, and no single pathogen has been convincingly implicated.

Socioeconomic and living conditions have been investigated less extensively and with weaker evidence. Some studies suggest higher risk among children from urban environments or higher socioeconomic status, reflecting the well-known "hygiene hypothesis" (a reduced exposure to infections in childhood contributes to an increased risk of allergic and autoimmune diseases[49,50]), but these observations have not been consistently replicated.

8. Future directions

The environmental landscape in JIA is characterized by weak-to-moderate associations, limited reproducibility, and considerable confounding factors. Therefore, in order to better understand the environmental determinants of JIA, there is a need of a shift from retrospective, population-based studies, to an integrated and longitudinal research approach. A significant step-up could be represented by the development of large birth cohorts with long-term follow-up in order to accurately measure exposures (such as dietary intake, pollutant levels, infection records, medication use, etc.) along with reliable microbiome, metabolomic, and epigenetic analyses. The integration of these data is essential to enable a clearer distinction between correlation and causation, aiming to draw specific preventive strategies. Moreover, microbiome-focused research should prioritize standardized sampling and sequencing pipelines along with functional analyses to better explore how microbiome disruption contributes to JIA development. Experimental models could also clarify whether specific microbial changes are causative or secondary to chronic inflammation. Studying gene-environment interactions could represent a key advancement for an improved understanding of the pathogenetic mechanisms beyond JIA. This approach requires harmonized datasets and collaborative consortia, possibly employing existing international networks such as PRINTO. Finally, the identification of environmental risk factors may open a world of possibilities for preventive interventions, such as strategies to minimize unnecessary antibiotic exposure in infancy (Table 2). However, such interventions must be based on robust causal evidence to avoid unintended effects.

Table 2
Summary of evidence on environmental factors in juvenile idiopathic arthritis development and clinical implications.

Environmental factors	Key message	Clinical implications
Prenatal factors	Associations weak and inconsistent	No robust evidence to recommend limiting fish intake during pregnancy
Perinatal factors	Limited evidence that caesarean delivery may slightly increase the risk of JIA, potentially via disruption of neonatal gut microbiota	No change in obstetric practice
Early-life factors	Observational evidence that antibiotic use in infancy may increase the risk of JIA, likely through perturbation of gut microbiota	Limit unnecessary antibiotic use, especially in early life
Socioeconomic and environmental factors	Associations weak and inconsistent	No actionable guidance currently

Abbreviations: juvenile idiopathic arthritis (JIA).

9. Conclusions

Current evidence supports the hypothesis that environmental factors contribute to JIA development, but the strength of these associations is modest, often inconsistent, and frequently confounded. The most coherent biological signal relates to early-life microbiome perturbation, particularly through early antibiotic exposure, while associations with perinatal events, socioeconomic conditions, and infections remain suggestive but not definitive. At the state of the art, the current evidence should be interpreted cautiously, avoiding oversimplified or causal claims.

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During the preparation of this work the authors used a Large Language Model to improve readability and for minor grammar corrections. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Abbreviations list

Enthesitis-related arthritis (ERA)
Juvenile idiopathic arthritis (JIA)
Pediatric Rheumatology INternational Trials Organization (PRINTO)

CRediT authorship contribution statement

Saverio La Bella: Writing – original draft, Data curation, Conceptualization. **Alessandra Alongi:** Writing – review & editing, Supervision, Conceptualization. **Giovanni Filocamo:** Writing – review & editing, Supervision, Conceptualization. **Marco Cattalini:** Writing – review & editing, Supervision, Conceptualization. **Stefano Lanni:** Writing – review & editing, Supervision, Conceptualization. **Achille Marino:** Writing – review & editing, Supervision, Conceptualization. **Francesca Minoia:** Writing – review & editing, Supervision, Conceptualization. **Nicolino Ruperto:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet*. 2007;369:767–778. https://doi.org/10.1016/S0140-6736(07)60363-8.

2. Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. *Jt Bone Spine*. 2014;81:112–117. https://doi.org/10.1016/j.jbspin.2013.09.003.
3. Martini A, Lovell DJ, Albani S, Brunner HI, Hyrich KL, Thompson SD, et al. Juvenile idiopathic arthritis. *Nat Rev Dis primers Nat Publ Group;*. 2022;8:5. https://doi.org/10.1038/s41572-021-00332-8.
4. Sandborg CI, Schulert GS, Kimura Y. Juvenile idiopathic arthritis. *N Engl J Med*. 2025;393:162–174. https://doi.org/10.1056/NEJMra2402073.
5. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004;31:390–392.
6. Martini A, Ravelli A, Avcin T, Beresford MW, Burgos-Vargas R, Cuttica R, et al. Toward new classification criteria for juvenile idiopathic arthritis: first steps, pediatric rheumatology international trials organization international consensus. *J Rheumatol*. 2019;46:190–197. https://doi.org/10.3899/jrheum.180168.
7. Cattalini M, Soliani M, Caparello MC, Cimaz R. Sex differences in pediatric rheumatology. *Clin Rev Allergy Immunol*. 2019;56:293–307. https://doi.org/10.1007/s12016-017-8642-3.
8. Berkun Y, Padeh S. Environmental factors and the geoepidemiology of juvenile idiopathic arthritis. *Autoimmun Rev*. 2010;9:A319–A324. https://doi.org/10.1016/j.autrev.2009.11.018.
9. Fujikawa S, Okuni M. Clinical analysis of 570 cases with juvenile rheumatoid arthritis: results of a nationwide retrospective survey in Japan. *Acta Paediatr Jpn*. 1997;39:245–249. https://doi.org/10.1111/j.1442-200x.1997.tb03593.x.
10. Arkachaisri T, Tang SP, Daengsuwan T, Phongsamart G, Vilaiyuk S, Charuvanij S, et al. Paediatric rheumatology clinic population in Southeast Asia: are we different? *Rheumatology*. 2017;56:390–398. https://doi.org/10.1093/rheumatology/kew446.
11. Consolaro A, Giancane G, Alongi A, van Dijkhuizen EHP, Aggarwal A, Al-Mayouf SM, et al. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study. *Lancet Child Adolesc Health*. 2019;3:255–263. https://doi.org/10.1016/S2352-4642(19)30027-6.
12. La Bella S, Rinaldi M, Di Ludovico A, Di Donato G, Di Donato G, Salpietro V, et al. Genetic background and molecular mechanisms of juvenile idiopathic arthritis. *Int J Mol Sci*. 2023;24. https://doi.org/10.3390/ijms24031846.
13. Clarke SLN, Mageean KS, Maccora I, Harrison S, Simonini G, Sharp GC, et al. Moving from nature to nurture: a systematic review and meta-analysis of environmental factors associated with juvenile idiopathic arthritis. *Rheumatoogy*. 2022;61:514–530. https://doi.org/10.1093/rheumatology/keab627.
14. Horton DB, Shenoi S. Review of environmental factors and juvenile idiopathic arthritis. *Open Access Rheumatol: Res Rev*. 2019;11:253–267. https://doi.org/10.2147/OARRR.S165916.
15. Ellis JA, Munro JE, Ponsonby AL. Possible environmental determinants of juvenile idiopathic arthritis. *Rheumatology*. 2010;49:411–425. https://doi.org/10.1093/rheumatology/kep383.
16. Degboe Y, Vastert SJ, Prakken BJ, McInnes IB. *How Does Age Determine the Development of Human Immune-Mediated arthritis? Nat Rev Rheumatol*. 18. Nature Publishing Group; 2022:501–512. https://doi.org/10.1038/s41584-022-00814-3.
17. Carlens C, Jacobsson L, Brandt L, Cnattingius S, Stephansson O, Askling J. Perinatal characteristics, early life infections and later risk of rheumatoid arthritis and juvenile idiopathic arthritis. *Ann Rheum Dis*. 2009;68:1159–1164. https://doi.org/10.1136/ard.2008.089342.
18. Bell SW, Shenoi S, Nelson JL, Bhatti P, Mueller BA. Juvenile idiopathic arthritis in relation to perinatal and maternal characteristics: a case control study. *Pediatr Rheumatol Online J*. 2017;15:36. https://doi.org/10.1186/s12969-017-0167-z.
19. Sperling CD, Kjaer SK, Hargreave M, Jensen A. Risk of juvenile idiopathic arthritis among children conceived after fertility treatment: a nationwide registry-based cohort study. *Hum Reprod*. 2019;34:1139–1145. https://doi.org/10.1093/humrep/dez035.
20. Chiaroni-Clarke RC, Munro JE, Pezic A, Cobb JE, Akikusa JD, Allen RC, et al. Association of increased sun exposure over the life-course with a reduced risk of juvenile idiopathic arthritis. *Photochem Photobiol*. 2019;95:867–873. https://doi.org/10.1111/php.13045.
21. Shenoi S, Bell S, Wallace CA, Mueller BA. Juvenile idiopathic arthritis in relation to maternal prenatal smoking. *Arthritis Care Res*. 2015;67:725–730. https://doi.org/10.1002/acr.22471.
22. Miller J, Ponsonby AL, Pezic A, Kemp A, Piper SE, Akikusa JD, et al. Sibling exposure and risk of juvenile idiopathic arthritis. *Arthritis Rheumatol*. 2015;67:1951–1958. https://doi.org/10.1002/art.39129.
23. Shenoi S, Shaffer ML, Wallace CA. Environmental risk factors and early-life exposures in juvenile idiopathic arthritis: a case-control study. *Arthritis Care Res (Hob)*. 2016;68:1186–1194. https://doi.org/10.1002/acr.22806.
24. França CMP, Sallum AME, Braga ALF, Strufaldi FL, Silva CAA, Farhat SCL. Risk factors associated with juvenile idiopathic arthritis: exposure to cigarette smoke and air pollution from pregnancy to disease diagnosis. *J Rheumatol*. 2018;45:248–256. https://doi.org/10.3899/jrheum.161500.
25. Kindgren E, Guerrero-Bosagna C, Ludvigsson J. Heavy metals in fish and its association with autoimmunity in the development of juvenile idiopathic arthritis: a prospective birth cohort study. *Pediatr Rheumatol Online J*. 2019;17:33. https://doi.org/10.1186/s12969-019-0344-3.
26. Dåstøl VØ, Haftorn KL, Rudsari HK, Jaholkowski PP, Størdal K, Håberg SE, et al. Maternal seafood intake, dietary contaminant exposure, and risk of juvenile idiopathic arthritis: exploring gene-environment interactions. *Front Immunol Front*. 2025:15. https://doi.org/10.3389/fimmu.2024.1523990.
27. Hestetun S, Andersen S, Sanner H, Størdal K. Antibiotic exposure in prenatal and early life and risk of juvenile idiopathic arthritis: a nationwide register-based cohort study. *RMD Open*. 2023;9, e003333. https://doi.org/10.1136/rmdopen-2023-003333.
28. Kristensen K, Henriksen L. Cesarean section and disease associated with immune function. *J Allergy Clin Immunol*. 2016;137:587–590. https://doi.org/10.1016/j.jaci.2015.07.040.
29. Radon K, Windstetter D, Poluda D, Häfner R, Thomas S, Michels H, et al. Exposure to animals and risk of oligoarticular juvenile idiopathic arthritis: a multicenter case-control study. *BMC Musculoskelet Disord*. 2010;11:73. https://doi.org/10.1186/1471-2474-11-73.
30. Berkun Y, Lewy H, Padeh S, Laron Z. Seasonality of birth of patients with juvenile idiopathic arthritis. *Clin Exp Rheumatol*. 2015;33:122–126.
31. Mason T, Rabinovich CE, Fredrickson DD, Amoroso K, Reed AM, Stein LD, et al. Breast feeding and the development of juvenile rheumatoid arthritis. *J Rheumatol*. 1995;22:1166–1170.
32. Ellis JA, Ponsonby AL, Pezic A, Chavez RA, Allen RC, Akikusa JD, et al. CLARITY - ChiLdhood arthritis risk factor identification sTudY. *Pediatr Rheumatol Online J*. 2012;10:37. https://doi.org/10.1186/1546-0096-10-37.
33. Rosenberg AM. Evaluation of associations between breast feeding and subsequent development of juvenile rheumatoid arthritis. *J Rheumatol*. 1996;23:1080–1082.
34. Kindgren E, Fredrikson M, Ludvigsson J. Early feeding and risk of juvenile idiopathic arthritis: a case control study in a prospective birth cohort. *Pediatr Rheumatol Online J*. 2017;15:46. https://doi.org/10.1186/s12969-017-0175-z.
35. Kindgren E, Ahrens AP, Triplett EW, Ludvigsson J. Infant gut microbiota and environment associate with juvenile idiopathic arthritis many years prior to disease onset, especially in genetically vulnerable children. *EBioMedicine*. 2023;93, 104654. https://doi.org/10.1016/j.ebiom.2023.104654.
36. Räisänen LK, Kääriäinen SE, Sund R, Engberg E, Viljakainen HT, Kolho KL. Antibiotic exposures and the development of pediatric autoimmune diseases: a register-based case–control study. *Pediatr Res Nat Publ Group*. 2023;93:1096–1104. https://doi.org/10.1038/s41390-022-02188-4.
37. Kindgren E, Ludvigsson J. Infections and antibiotics during fetal life and childhood and their relationship to juvenile idiopathic arthritis: a prospective cohort study. *Pediatr Rheumatol*. 2021;19:145. https://doi.org/10.1186/s12969-021-00611-4.
38. Arvonen M, Virta LJ, Pokka T, Kröger L, Vähäsalo P. Repeated exposure to antibiotics in infancy: a predisposing factor for juvenile idiopathic arthritis or a sign of this group's greater susceptibility to infections? *J Rheumatol*. 2015;42:521–526. https://doi.org/10.3899/jrheum.140348.
39. Horton DB, Scott FI, Haynes K, Putt ME, Rose CD, Lewis JD, et al. Antibiotic exposure and juvenile idiopathic arthritis: a case–Control study. *Pediatrics*. 2015;136:e333–e343. https://doi.org/10.1542/peds.2015-0036.
40. McDonnell L, Gilkes A, Ashworth M, Rowland V, Harries TH, Armstrong D, et al. Association between antibiotics and gut microbiome dysbiosis in children: systematic review and meta-analysis. *Gut Microbes Taylor Fr;*. 2021;13, 1870402. https://doi.org/10.1080/19490976.2020.1870402.
41. Stocker M, Klingenberg C, Navér L, Nordberg V, Berardi A, El Helou S, et al. Less is more: antibiotics at the beginning of life. *Nat Commun*. 2023;14:2423. https://doi.org/10.1038/s41467-023-38156-7.
42. Nielsen HE, Dørup J, Herlin T, Larsen K, Nielsen S, Pedersen FK. Epidemiology of juvenile chronic arthritis: risk dependent on sibship, parental income, and housing. *J Rheumatol*. 1999;26:1600–1605.
43. Saçkesen C, Kocabıyık KP, Medina E. Binbaşaran Tüysüzoğlu B. Climate crisis and its impacts on health "the future is now. *Turk Arch Pediatr*. 2025;60:248–250. https://doi.org/10.5152/TurkArchPediatr.2025.1112253.
44. Kunnamo I. Infections and related risk factors of arthritis in children. A case-control study. *Scand J Rheumatol*. 1987;16:93–99. https://doi.org/10.3109/03009748709102913.
45. Aslan M, Kasapcopur O, Yasar H, Polat E, Saribas S, Cakan H, et al. Do infections trigger juvenile idiopathic arthritis? *Rheumatol Int*. 2011;31:215–220. https://doi.org/10.1007/s00296-009-1253-4.
46. Angelini F, Cancrini C, Colavita M, Panei P, Concato C, Romiti ML, et al. Role of parvovirus B19 infection in juvenile chronic arthritis. Is more investigation needed? *Clin Exp Rheumatol*. 2003;21:684.
47. González B, Larrañaga C, León O, Díaz P, Miranda M, Barria MA, et al. Parvovirus B19 may have a role in the pathogenesis of juvenile idiopathic arthritis. *J Rheumatol*. 2007 Jun;34(6):1336–1340.
48. Roszkiewicz J, Lach J, Baranowska M, Strapagiel D, Wyka K, Smolewska E. The intestinal microbiome in juvenile idiopathic arthritis-results of a single-center pilot study from Poland. *J Clin Med*. 2025;14:6038. https://doi.org/10.3390/jcm14176038.
49. Bach JF. The hygiene hypothesis in autoimmunity: the role of pathogens and commensals. *Nat Rev Immunol*. 2018;18:105–120. https://doi.org/10.1038/nri.2017.111.
50. Kıykım A, Öğülür İ, Yazıcı D, Çokuğraş H, Akdiş M, Akdiş CA. Epithelial barrier hypothesis and its comparison with the hygiene hypothesis. *Turk Arch Pediatr*. 2023;58:122–128. https://doi.org/10.5152/TurkArchPediatr.2023.23006.