Systematic review and meta analysis

Moving from nature to nurture: a systematic review and meta-analysis of environmental factors associated with juvenile idiopathic arthritis

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Abstract

Objectives. JIA is the most common paediatric rheumatic disease, thought to be influenced by both genetics and the environment. Identifying environmental factors associated with disease risk will improve knowledge of disease mechanism and ultimately benefit patients. This review aimed to collate and synthesize the current evidence of environmental factors associated with JIA.

Methods. Four databases (MEDLINE, Embase, Web of Science and Cumulative Index to Nursing and Allied Health Literature) were searched from inception to January 2020. Study quality was rated using the Newcastle-Ottawa Scale. Pooled estimates for each environmental factor were generated using a random-effects, inverse-variance method, where possible. The remaining environmental factors were synthesized in narrative form.

Results. This review includes 66 environmental factors from 39 studies (11 cohort and 28 case-control studies) over 45 years. Study sample sizes ranged from 41 to 1.9 million participants. Eight environmental factors from ten studies were meta-analysed. Caesarean section delivery was associated with increased JIA risk [pooled odds ratio (OR) 1.11, 95% CI: 1.01, 1.22]. Conversely, presence (vs absence) of siblings (pooled OR 0.60, 95% CI: 0.44, 0.81) and maternal prenatal smoking (pooled OR 0.70, 95% CI: 0.58, 0.84) were associated with decreased JIA risk.

Conclusion. This review identifies several environmental factors associated with JIA and demonstrates the huge breadth of environmental research undertaken over five decades. We also highlight the challenges of combining data collected over this period due to limited between study comparability, evolution in healthcare and social practices, and changing environment, which warrant consideration when planning future studies.

Key words: juvenile idiopathic arthritis, risk factor, environmental

Rheumatology key messages

- Despite being a complex disease, robust evidence of environmental associations of JIA incidence is limited.
- We identified strong evidence of environmental factors associated with both increased and decreased JIA risk.
- The findings of this study will inform (causal) research and contribute to understanding JIA aetiopathogenesis.

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Introduction

JIA is the most common rheumatic disease of childhood with a pooled prevalence of 32.6/100 000 in Caucasians [1]. International consensus criteria currently define seven subtypes of JIA based on their clinical features [2]; however, diagnostic criteria have evolved over the years [3]. JIA is considered a complex disease influenced by both non-Mendelian genetics and the environment. The genetic contribution to JIA, examined both in familial studies and in genome-wide association studies, has been estimated to be between 13% and 32% [4–7]. A substantial contribution to disease risk is likely attributed to gene-environment interactions and environmental factors.

Studies of other autoimmune diseases demonstrate the potential for environmental exposures to induce epigenetic changes [8], modulate the immune system [9] or alter the microbiome [10]. While the role of environmental factors in JIA is less clear, it is likely that similar mechanisms influence JIA risk. Two narrative reviews of environmental factors associated with JIA have been published in recent years [11, 12] that highlight several key limitations of research to date. Firstly, the availability of high-quality data in JIA is limited, often of modest sample size and lags behind that of other autoimmune conditions. Secondly, many environmental factors studied so far, such as breastfeeding, infection and smoking, require further scrutiny. Finally, several environmental factors, such as diet, remain relatively unexplored.

Identifying environmental factors associated with JIA, and quantifying their effects, has the potential to benefit patients by guiding research priorities and informing future studies probing causality and disease mechanism. Such developments could inform new therapeutic modalities and assist in patient counselling and risk stratification. Finally, environmental associations may be readily and/or feasibly modifiable, which could translate into lower disease burden within populations.

The aim of this systematic review and meta-analysis was to collate, quantify and evaluate the current evidence for environmental factors that influence JIA risk and highlight areas of unmet research need.

Methods

This review follows guidance from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [13] and the protocol was pre-registered on PROSPERO (ID: CRD42017078306) [14].

Literature searching

Expert advice from a literature searching specialist was sought prior to designing the search strategy. A systematic search of MEDLINE (Ovid), Embase (Ovid), Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCOHost) and Web of Science (WOS, Clarivate Analytics) was performed, with English language restriction, from database inception to January 2020. The MEDLINE search strategy (Table 1) was amended for use in other databases (Supplementary Table S1, available at Rheumatology online). Bibliographies of excluded review articles were hand-searched to identify further relevant studies.

Study selection

All aspects of study selection and risk of bias assessment were undertaken independently by two reviewers (S.L.N.C. and either K.S.M. or I.M.). Any discrepancies were resolved by discussion then involvement of an additional reviewer (A.V.R.). References were downloaded into Endnote (version X9.3.2, Clarivate Analytics) and de-duplicated as recommended [15]. Blind title and abstract screening was performed using Rayyan (QCRI) [16] against the inclusion/exclusion criteria (Table 2). The full texts of potentially relevant studies were retrieved and further reviewed against the inclusion/exclusion criteria.

Data extraction

Data items (Supplementary Table S2, available at Rheumatology online) were extracted from each included study by S.L.N.C. into a predesigned template. This was independently checked by either K.S.M. or I.M., with involvement of an additional reviewer (A.V.R.) where necessary. Where a study included multiple case or control groups, data was extracted from (i) the most matched case and control groups and (ii) community
control groups in preference to hospital control groups. Corresponding authors were contacted to obtain missing data or clarify data ambiguities.

Risk of bias (quality) assessment

We used the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies to assess the risk of bias and methodological quality of included studies [17]. The scale scores three study domains (selection criteria, comparability and outcome) with a maximum score of nine indicating the highest quality. A risk of biases table was created, summarizing study quality.

Data synthesis and statistical analysis

Data was analysed using the statistical software R (version 3.6.1) in RStudio. The data was synthesized into ten environmental factor ‘domains’ (maternal, paternal, perinatal, early life, smoking, environmental, socioeconomic, living environment, dietary and infections). For consistency, unadjusted odds ratios (OR) and 95% CI were derived for all variables where sufficient raw data was available. To aid synthesis, the data was condensed in two ways. Firstly, although all relevant data reported by a study was extracted, only the most inclusive evidence for each environmental factor from each study was included in our synthesis, as jointly determined by S.L.N.C. and A.V.R. For example, sex-stratified or JIA subtype specific analyses were not included in the narrative synthesis where a mixed-sex or pan-JIA subtype analysis, respectively, was reported. Secondly, a single point estimate with 95% CI was reported for each variable from each study. This consisted of, in order of priority and subject to data availability, the most adjusted point estimate, the derived unadjusted estimate or the study reported unadjusted estimate. Our complete dataset is included in Supplementary Table S3, available at Rheumatology online, illustrating the data inclusion decisions. Forest plots were constructed summarizing a single point estimate with 95% CI for each environmental factor. Pooled ORs were generated for environmental factors examined in multiple studies in a comparable manner (clinically and statistically). Where possible, ordinal categorical data was converted to a single estimate using generalized least squares of trend [18] implemented in the glst module [19] in Stata (version 14.2) prior to meta-analysis (Supplementary Data S1, available at Rheumatology online). Only studies reporting adjusted estimates were included in meta-analysis. All meta-analyses used the inverse weighted variance method in the meta R package using a random effects model. Statistical heterogeneity was assessed using Cochran’s Q test ($\chi^2$ test) and Higgin’s $I^2$ value [20].

Results

Study selection

Literature searches identified 5933 unique database records (Fig. 1A). The majority (5731/5933) were excluded during title and abstract screening. Of the 202 full-text records examined, 39 studies met the pre-specified inclusion criteria.

Study characteristics

Table 3 details the 11 cohort and 28 case-control studies included in this review. Studies originate from 13 countries and were published between 1974 and 2019. Sample sizes ranged from 41 to 1 900 000 participants. JIA cases from mixed-sex studies were predominantly female (range 52.6–81.5% female); four studies were restricted to single-sex participants [21-24]. Studies differed considerably in overall design, encompassing nine different versions of JIA diagnostic criteria and variable inclusivity of JIA subtypes. Most studies (23/39)
Fig. 1 PRISMA flow diagram for study selection (A) and results of meta-analysis (B)

(A) PRISMA flow diagram showing the selection of studies included in this review. CINAHL: Cumulative Index to Nursing and Allied Health Literature; PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; WOS, Web of Science. (B) Meta-analysis results of studies examining associations between JIA and perinatal, early life, maternal and smoking related factors. OR: odds ratio.
| Study | Study type | Country | Sample size | Age range (years) | Sex (female, %) | JIA criteria used | JIA subtypes included | Risk factors examined | Matching of controls |
|-------|------------|---------|-------------|------------------|-----------------|------------------|----------------------|----------------------|---------------------|
| Cassidy, 1974 [54] | Case-control | USA | 131 cases/80 controls | 2–18 | 66.4 | ACR 1973 | No exclusions reported | Rubella, rubeola | No |
| Chantler, 1985 [55] | Case-control | Canada | 19 cases/8 controls | 8–20 | 52.6 | ACR 1977 | No exclusions reported | Rubella | No |
| Kunnamo, 1987 [46] | Case-control | Finland | 26 cases/26 controls | <16 years | | ACR 1977 | No exclusions reported | Upper respiratory tract infection, daycare spondyloarthropathies | |
| Mason, 1995 [43] | Case-control | USA | 54 cases/79 controls | 5.4 (±3.8) | 81.5 | ACR 1977 | Excluded | Date of birth, sex, geography | Breastfeeding |
| Tsai, 1995 [53] | Case-control | China | 21 cases/20 controls | 13a | | ACR 1977 | No exclusions reported | CMV, EBV | Age |
| Rosenberg, 1996 [44] | Case-control | Canada | 137 cases/331 controls | | | ACR 1977 | No exclusions reported | Breastfeeding, cow’s milk | No (parent selected) |
| Nielsen, 1999 [37] | Case-control | Denmark | 220 cases/880 controls | 6b | | EULAR 1978 | Excluded | Siblings, income, residential factors, parental employment/occupation, season of birth | |
| Angelini, 2003 [50] | Case-control | Italy | 35 cases/93 controls | 2.0–14 | 75.6 | ACR 1987 | All | Parvovirus B19 | Sex |
| Lehmann, 2003 [51] | Case-control | Germany | 68 cases/124 controls | | | ILAR 1997 | No exclusions reported | Parvovirus B19 | Age |
| Prahalad, 2003 [40] | Case-control | USA | 333 cases/3295 controls | 61.86 | 61.9 | ILAR 1997 | No exclusions reported | Siblings, birth order | Sex, birth year |
| Altun, 2004 [48] | Case-control | Turkey | 60 cases/35 controls | 1.16–15.6 | 68.3 | ILAR 1997 | Excluded | Chlamydia pneumoniae | Age |
| Jaakkola, 2005 [25] | Retrospective cohort | Finland | 58 841 | | 74.2 | ICD-9 | Code 714.3 | Birth weight, size for gestational age, maternal age, parity, maternal civil status, parental employment/occupation, maternal prenatal smoking | n/a |
| Gonzalez, 2007 [52] | Case-control | Chile | 50 cases/39 controls | 0.5–12 | 60.0 | ILAR 1997, EULAR 1978, ACR 1977 | No exclusions reported | Parvovirus B19 | No |

(continued)
### Table 3

| Study          | Study type       | Country   | Sample size          | Age range (years) | Sex (female, %) | JIA criteria used | JIA subtypes included | Risk factors examined                                                                                       | Matching of controls |
|----------------|------------------|-----------|----------------------|-------------------|-----------------|-------------------|-----------------------|----------------------------------------------------------------------------------------------------------|----------------------|
| Carlens, 2009  | Case-control     | Sweden    | 3334 cases/13 336 controls | 3b                | 54.0            | ICD8-10           | ICD codes not listed | Maternal age, maternal civil status, siblings, season of birth, mode of delivery, type of birth, birth weight, size for gestational age, gestational age, congenital malformation, maternal smoking, apgar score at 5 min, infections in first year of life | Age, sex, hospital of birth |
| Radon, 2010    | Case-control     | Germany   | 238 cases/832 controls | 10.9 (±3.1)a      | 71.4            | ILAR 2001         | Oligo only            | Parental education, breastfeeding, birth weight, maternal prenatal smoking, residential factors, daycare, allergy, pets/animals | No                   |
| Aslan, 2011    | Case-control     | Turkey    | 26 cases/24 controls  | 1.58–4.58         | 69.2            | ILAR 1997         | Excluded ERA and HLA-B27+ patients | Mycoplasma pneumoniae, Borrelia burgdorferi, Chlamydia pneumoniae, Chlamydia trachomatis, Campylobacter jejuni, EBV, Parvovirus B19, culture positive | No                   |
| Bager, 2012    | Retrospective cohort | Denmark   | 924 749             |                   |                 | ICD-10            | Codes M08.0, M08.2, M08.3, M08.4, M08.8, M08.9 | Mebendazole          | n/a                                                             |
| Ellis, 2012    | Case-control     | Australia | 229 cases/458 controls | 9.4 (±4.6)a       | 68.1            | ILAR 2001         | No exclusions reported | Socioeconomic status, parental education, maternal civil status, parental employment/occupation, maternal smoking, maternal age, maternal prenatal smoking, diet/supplement use during pregnancy, paternal civil status, paternal smoking, paternal age, | Cases matched to geographical controls |

(continued)
| Study | Study type | Country | Sample size | Age range (years) | Sex (female, %) | JIA criteria used | JIA subtypes included | Risk factors examined | Matching of controls |
|-------|------------|---------|-------------|------------------|-----------------|-----------------|----------------------|----------------------|---------------------|
| Neufeld, 2013 [41] | Case-control | Canada | 373 cases/987 controls | 8.1 (male), 10.7 (female) | 66.2 | ILAR 2001, ACR 1977 | Excluded psoriatic and IBD related | Stressful life events, residential factors | Age, sex, geography |
| Arnheim-Dahlstrom, 2013 [22] | Retrospective cohort | Denmark, Sweden | 10–17 | 100.0 | ICD-10 | ICD codes M08.0, M08.2-9 | | HPV vaccination | n/a |
| Arvonen, 2015 [58] | Case-control | Finland | 1298 cases/5179 controls | 0.8–12.9 | 63.3 | ICD-10 | ICD code M08 | Antibiotic use | Age, sex, geography |
| Berkun, 2015 [38] | Case-control | Israel | 558 cases/1040 controls | 67.6 | ILAR 2001 | All | | Season of birth | No |
| Sevelsted, 2015 [35] | Retrospective cohort | Denmark | 1 900 000 | | ICD-8 and ICD-10 | Codes 712.00 (ICD-8) and M05.x, M08x, M09x, M13.x (ICD-10) | | Mode of delivery | n/a |
| Miller, 2015 [39] | Case-control | Australia | 302 cases/341 controls | 8.5 (±4.7) | 66.9 | ILAR 2001 | Excluded systemics | Birth order, siblings | Geography |
| Shenoi, 2015 [47] | Case-control | USA | 1196 cases/5618 controls | <16 years | 67.7 | ILAR 2001 | No exclusions reported | Maternal prenatal smoking | Birth year, geography |
| Haerskjold, 2016 [57] | Retrospective cohort | Denmark, Sweden | 1 351 265 | | ICD-10 | Codes M08, M09 | | Palivizumab | n/a |
| Kristensen, 2016 [36] | Retrospective cohort | Denmark | 790 569 | 0–14 | ICD-10 | Codes M08.0-M08.9 | | Mode of delivery | n/a |
| Shenoi, 2016 [28] | Case-control | USA | 225 cases/138 controls | <16 years | 70.7 | ILAR 2001 | No exclusions reported | Income, birth weight, mode of delivery, gestational age, BMI at time of survey, household smoking, maternal prenatal smoking, duration prenatal smoking, months, maternal smoking, paternal smoking, relative smoking, breastfeeding, cow’s milk, infections in first year of life, daycare, birth order, stressful life events, maternal age, paternal smoking, breastfeeding, cow’s milk, mode of delivery | Age, sex | (continued) |
### Table 3 Continued

| Study          | Study type     | Country   | Sample size                  | Age range (years) | Sex (female, %) | JIA criteria used | JIA subtypes included | Risk factors examined                                                                 | Matching of controls                        |
|----------------|----------------|-----------|------------------------------|-------------------|----------------|-------------------|-----------------------|----------------------------------------------------------------------------------------|---------------------------------------------|
| Arvonen, 2017  | Case-control   | Finland   | 1298 cases/5179 controls    | 0.7–13            | 63.3           | ICD-10, ILAR 2001 | ICD10 codes M08       | Cow’s milk, antibiotic use, combined effect of cow’s milk allergy and antibiotics      | 4:1 based on age, sex, municipality of residence                                        |
| Bell, 2017 [30] | Case-control   | USA       | 1252 cases/6072 controls    | <16 years         | 67.3           | ILAR 2001         | No exclusions reported | Type of birth, gestational age, size for gestational age, birth weight, mode of delivery, no of prior births, foetal loss | Birth year, geography                                                                    |
| Kindgren, 2017 | Case-control   | Sweden    | 32 cases/10 883 controls    |                   |                | ICD8-10           | Codes M08-09          | Breastfeeding, cow’s milk, introduction of gluten                                         | No                                                                                       |
| Thorsen, 2017  | Case-control   | Denmark   | 300 cases/300 controls      | 3–9               | 69.7           | ILAR 1997, ILAR 2001, EULAR 1978 | Included oligo and poly only (RF+/−)       | Vitamin D, gestational age, birth weight, maternal age                                   | Date of birth                                                                            |
| Franca, 2018   | Case-control   | Brazil    | 66 cases/124 controls       | 10.8 (± 3.9)\(^a\) | 59.1           | ILAR 2001         | No exclusions reported | Socioeconomic status, prenatal pollution exposure, maternal prenatal smoking, maternal weight gain in pregnancy, diet/supplement use during pregnancy, gestational age, birth weight, season of pregnancy, smoke exposure, daycare, pollution exposure | Age, sex                                                                                   |
| Skufca, 2018   | Retrospective cohort | Finland | 240 605                     | 100.0             |                | ICD-10            | ICD code M080, M082, M083, M084, M089 | HPV vaccination                                                                          | n/a                                                                                       |
| Frisch, 2018   | Retrospective cohort | Denmark | 568 410                     | 0.0               |                | ICD-10            | ICD codes M08,0, M08,2-9 | HPV vaccination                                                                          | n/a                                                                                       |
| Liu, 2018 [23] | Retrospective cohort | Canada   | 290 939                     | 100.0             |                | ICD-9, ICD-10     | ICD-9 codes 711, 714, 715 and ICD-10 codes M05, M06, M08 | HPV vaccination                                                                          | n/a                                                                                       |
undertook covariate adjustment and 20/28 case-control studies matched cases and controls.

Risk of bias

Included studies were of variable quality; NOS scores ranged from two to nine. Cohort studies were of higher quality than case-control studies overall (mean NOS score 6.6 vs 4.4, Tables 4 and 5). Scores were commonly downgraded for lack of independent validation of case status (case-control studies), inadequacy of follow up (cohort studies) and limited confounder adjustment.

Evidence synthesis

Sixty-six environmental factors were examined within this review of which half were only examined in a single study. Forty-five environmental factors had both covariate unadjusted and adjusted analyses; covariate unadjusted and adjusted data was available for 63 and 48 environmental factors, respectively. Eight environmental factors from ten studies were meta-analysed (Fig. 1B) with the remainder summarized in narrative form (Supplementary Fig. S1A–1J, available at Rheumatology online). Supplementary Table S3, also available at Rheumatology online, details all estimates extracted/derived for each study.

Maternal factors

Maternal factors were examined in nine studies [25–33] (Supplementary Fig. S1A, available at Rheumatology online). Meta-analysis of four studies [25–27, 29] found no evidence of an association between JIA and maternal age (pooled OR 1.02, 95% CI: 0.99, 1.05, Fig. 1B). There was some evidence of a protective association between maternal multiparity and JIA [25, 30], albeit with imprecise estimates. One study [27] identified maternal civil status (married) as associated with increased JIA risk (OR 2.62, 95% CI: 1.16, 5.92), however this was unsupported by other studies [25, 26, 28]. Of the maternal dietary factors examined [27, 32, 33], only the consumption of fish more than once a week during pregnancy showed strong evidence of association with JIA (OR 4.50, 95% CI: 1.90, 10.40) in a single study [33]. Maternal fertility problems [31], but not prior foetal loss [30] or specific fertility treatment [31], was associated with increased JIA risk (hazard ratio (HR) 1.18, 95% CI: 1.05, 1.32).

Paternal factors

Compared with maternal factors, there was little data regarding paternal factors associated with offspring JIA (Supplementary Fig. S1B, available at Rheumatology online). Two studies [27, 28] examining paternal age found no association with JIA. One study [27] found increased JIA risk associated with paternal civil status (OR 2.48, 95% CI: 1.06, 5.8), consistent with the corresponding maternal estimate.
| Study                  | Selection                     | Comparability                        | Exposure                     | Total |
|------------------------|-------------------------------|--------------------------------------|------------------------------|-------|
|                        | Adequate case definition with independent validation | Cases obviously representative | Selection of community control participants | Controls have no history of disease outcome | Study controls for socio-economic status | Study controls for maternal age | Source of ascertainment | Same method of ascertaining for cases and controls | Non response rate same for both groups |       |
| Cassidy, 1974 [54]    | 0                             | 0                                    | 1                            | 1     | 0     | 0     | 1     | 0     | 1     | 1     | 5     |
| Chantler, 1985 [55]   | 0                             | 0                                    | 0                            | 0     | 0     | 0     | 1     | 0     | 1     | 4     |
| Kunnamo, 1987 [46]    | 1                             | 1                                    | 1                            | 0     | 0     | 0     | 0     | 1     | 1     | 4     |
| Tsai, 1995 [53]       | 0                             | 0                                    | 0                            | 1     | 0     | 0     | 0     | 0     | 0     | 2     |
| Mason, 1995 [43]      | 0                             | 0                                    | 0                            | 1     | 0     | 0     | 0     | 1     | 0     | 2     |
| Rosenberg, 1996 [44]  | 0                             | 1                                    | 1                            | 1     | 0     | 0     | 0     | 1     | 0     | 4     |
| Nielsen, 1999 [37]    | 1                             | 1                                    | 1                            | 0     | 1     | 1     | 0     | 1     | 1     | 4     |
| Angelini, 2003 [50]   | 0                             | 0                                    | 0                            | 1     | 0     | 0     | 0     | 1     | 1     | 4     |
| Lehmann, 2003 [51]    | 0                             | 1                                    | 0                            | 1     | 0     | 1     | 1     | 1     | 1     | 4     |
| Prahalad, 2003 [40]   | 1                             | 1                                    | 0                            | 1     | 0     | 0     | 0     | 1     | 1     | 4     |
| Altun, 2004 [48]      | 0                             | 0                                    | 0                            | 1     | 0     | 0     | 0     | 1     | 1     | 4     |
| Gonzalez, 2007 [52]   | 1                             | 1                                    | 1                            | 0     | 0     | 0     | 1     | 0     | 1     | 1     |
| Carlens, 2009 [26]    | 0                             | 1                                    | 0                            | 0     | 1     | 1     | 1     | 0     | 1     | 6     |
| Radon, 2010 [34]      | 0                             | 1                                    | 0                            | 0     | 1     | 0     | 0     | 1     | 1     | 4     |
| Aslan, 2011 [49]      | 0                             | 0                                    | 0                            | 1     | 0     | 0     | 1     | 0     | 1     | 4     |
| Ellis, 2012 [27]      | 0                             | 0                                    | 0                            | 1     | 0     | 0     | 0     | 1     | 0     | 3     |
| Neufeld, 2013 [41]    | 0                             | 1                                    | 1                            | 0     | 0     | 1     | 0     | 1     | 0     | 3     |
| Avononen, 2015 [58]   | 0                             | 1                                    | 1                            | 1     | 0     | 0     | 1     | 1     | 1     | 6     |
| Berknun, 2015 [38]    | 0                             | 0                                    | 0                            | 1     | 0     | 1     | 0     | 0     | 1     | 1     |
| Miller, 2015 [59]     | 0                             | 0                                    | 0                            | 1     | 0     | 0     | 0     | 0     | 1     | 4     |
| Shenoi, 2015 [47]     | 1                             | 0                                    | 1                            | 1     | 0     | 1     | 0     | 0     | 1     | 5     |
| Shenoi, 2016 [28]     | 0                             | 1                                    | 1                            | 1     | 0     | 1     | 0     | 0     | 1     | 4     |
| Arvonen, 2017 [42]    | 0                             | 1                                    | 1                            | 1     | 0     | 1     | 1     | 1     | 1     | 6     |
| Bell, 2017 [30]       | 1                             | 0                                    | 1                            | 1     | 0     | 1     | 0     | 1     | 1     | 6     |
| Kindgren, 2017 [45]   | 1                             | 1                                    | 1                            | 0     | 1     | 1     | 0     | 0     | 1     | 6     |
| Thorsen, 2017 [29]    | 0                             | 0                                    | 1                            | 0     | 1     | 1     | 0     | 1     | 0     | 4     |
| Franca, 2018 [32]     | 0                             | 1                                    | 1                            | 1     | 0     | 0     | 0     | 1     | 0     | 6     |
| Chiaroni-Clarke, 2019 [59] | 1                             | 1                                    | 0                            | 1     | 1     | 1     | 0     | 0     | 1     | 6     |
Table 5: Newcastle-Ottawa Scale risk of bias assessment scores for cohort studies

| Study ID        | Selection | Comparability | Outcome | Total |
|-----------------|-----------|---------------|---------|-------|
|                 | Representativeness of exposed cohort | Non-exposed cohort from same community as exposed cohort | Source of ascertainment | Outcome of interest not present at start of study | Study controls for socio-economic status | Study controls for maternal age | Assessment of outcome | Follow up long enough for outcome to occur | Adequacy of follow up | Complete follow up or description provided of loss to follow-up |
|                 | Truly     | Somewhat      | Secure recorded | Blinded interview |                   |                       |                     |                       |                   |                                 |
| Jaakkola, 2005 [25] | 1 0 1 1 0 1 1 1 | 0 1 0 0 | 1 | 8 |
| Bager, 2012 [56]   | 1 0 1 1 0 1 1 1 | 0 1 0 0 | 7 |
| Arnheim-Dahlstrom, 2013 [22] | 0 1 1 1 0 1 1 1 | 0 1 0 0 | 7 |
| Sevelsted, 2015 [35] | 0 1 1 1 0 1 1 1 | 0 1 0 0 | 6 |
| Haerskjold, 2016 [57] | 0 1 1 1 0 1 1 1 | 0 1 0 0 | 5 |
| Kristensen, 2016 [36] | 0 1 1 1 0 1 1 1 | 0 1 0 0 | 6 |
| Frisch, 2018 [24]   | 1 0 1 1 0 1 1 1 | 0 1 0 0 | 6 |
| Liu, 2018 [23]      | 1 0 1 1 0 1 1 1 | 0 1 0 0 | 5 |
| Skulca, 2018 [21]   | 1 0 1 1 0 1 1 1 | 0 1 0 0 | 5 |
| Kindgren, 2019 [33] | 1 0 1 1 0 1 1 1 | 0 1 0 0 | 8 |
| Sperling, 2019 [31] | 1 0 1 1 0 1 1 1 | 0 1 0 0 | 9 |
Perinatal factors

Perinatal factors were examined in 11 studies [25–30, 32, 34–37] (Supplementary Fig. S1C, available at Rheumatology online). Six perinatal factors were included in the meta-analysis: pre and post-term delivery, small size for gestational age (SGA), low and high birth weight (LBW and HBW) and Caesarean section delivery (CSD). The pooled estimate from three studies [26, 28, 30] identified strong evidence that CSD is a risk factor for JIA (OR 1.11, 95% CI: 1.01, 1.22). Sevelsted et al. [35] also reported increased JIA risk following CSD (adjusted incidence rate ratio (IRR) 1.10, 95% CI: 1.02, 1.18) as did Kristensen and Henriksen [36] for elective (adjusted HR 1.25, 95% CI: 1.04, 1.51) but not acute CSD (adjusted HR 0.99, 95% CI: 0.82, 1.20). Evidence of association between instrumental delivery and JIA was inconsistent [27, 28]. The pooled estimates from four studies [26, 28–30] found little evidence of an association between JIA and pre- or post-term delivery (OR 1.03, 95% CI: 0.70, 1.54 and OR 1.02, 95% CI: 0.81, 1.27 respectively). Little evidence of association was found between JIA and birth weight [25, 26, 28–30, 34] (pooled OR 0.91 95% CI: 0.71, 1.16 and OR 0.94 95% CI: 0.83, 1.05 for LBW and HBW, respectively). Similarly, there was little evidence of association between JIA and SGA [25, 30] (pooled OR 1.37, 95% CI: 0.52, 3.57). Evidence from single studies suggests that ideal or less than ideal maternal weight gain during pregnancy [32] and Apgar score <6 [26] at delivery are negatively associated with JIA. One study [38] reported a distinct pattern in month of birth of JIA patients (with peak in November to March) vs the general population but this was unsupported by other studies examining season of birth or pregnancy [26, 32, 37]. There was little evidence of association between JIA and multiple birth [26, 30], neonatal vitamin D levels [29] and congenital malformation [26].

Early life factors

Five studies [26, 28, 37, 39, 40] examined the association between JIA and sibling-related factors (Supplementary Fig. S1D, available at Rheumatology online). Meta-analysis of two studies [37, 39] found strong evidence that having siblings was associated with decreased JIA risk (pooled OR 0.60, 95% CI: 0.44, 0.81). Though the association between JIA and ≥3 siblings was attenuated (pooled OR 0.81, 95% CI: 0.55, 1.19) [26, 39] and there was limited evidence of a dose-dependent association between JIA and sibling number [26, 39, 40]. Evidence of an association between JIA and birth order was inconsistent [28, 39, 40]. One study associated child obesity (BMI >30) with increased risk JIA (adjusted OR 3.98, 95% CI: 1.82, 8.34) but evidence was limited for other BMI categories [28]. Two studies examined the number and type of stressful life events [28, 41] with largely inconsistent estimates; for example, household unemployment [28] and maternal employment outside of the home [41] showed opposing effects (adjusted OR 0.23, 95% CI: 0.09, 0.59 and adjusted OR 0.65, 95% CI: 0.47, 0.90, respectively). The association between allergy and JIA was also conflicting; unadjusted OR 1.59, 95% CI: 1.19, 2.13 for cow’s milk allergy [42] and unadjusted OR 0.57, 95% CI: 0.34, 0.95 for allergic rhinitis [34].

Dietary factors

Seven studies [27, 28, 33, 34, 43–45] examined dietary factors (Supplementary Fig. S1E, available at Rheumatology online). Breastfeeding was the most frequently investigated dietary factor but there is little evidence of a consistent association between breastfeeding status [27, 28, 44, 45] or duration [27, 28, 34, 43, 45] and JIA. Similarly, there is little evidence of association between JIA and age of introduction of cow’s milk [27, 28, 44, 45] or gluten [45]. One study associated the consumption of fish more than once a week during the first year of life with increased JIA risk (adjusted OR 5.10, 95% CI: 2.10, 12.40), in keeping with their maternal data [33].

Living environment

Six studies [28, 32, 34, 37, 41, 46] examined factors associated with residential and family environment (Supplementary Fig. S1F, available at Rheumatology online). One study found day-care attendance was strongly associated with decreased JIA risk (adjusted OR 0.12, 95% CI: 0.04, 0.44) [32]; however, this was unsupported by others [28, 34, 46]. There was little consistent evidence of association between residential area and JIA; the strongly positive association between living in a flat (vs a farm) and JIA (adjusted OR 2.69, 95% CI: 1.19) [37] was unsupported by residential area data from other studies [28, 34, 41] or data regarding early life contact with animals/pets [28, 34].

Socioeconomic factors

Socioeconomic factors were examined in six studies [25, 27, 28, 32, 34, 37] (Supplementary Fig. S1G, available at Rheumatology online). In single studies, JIA was associated with higher maternal education (adjusted OR 2.72, 95% CI: 1.19, 6.20) [27] and higher household income (adjusted OR 1.94, 95% CI: 1.23, 3.07) [37]; however, little evidence of association was seen between JIA and other socioeconomic factors.

Smoking-related factors

Smoking behaviours were examined in seven studies [25–28, 32, 34, 47] (Supplementary Fig. S1H, available at Rheumatology online). Meta-analysis of four studies [27, 28, 34, 47] found strong evidence of a negative association between maternal prenatal smoking and JIA (pooled OR 0.70, 95% CI: 0.58, 0.84), with one study [27] also reporting a negative association between JIA and paternal prenatal smoking (adjusted OR 0.46, 95% CI: 0.21, 0.99). One study implied a dose-dependent relationship with higher levels of prenatal smoking.
decreasing the likelihood of JIA [47], this was unsupported by three further studies [25, 28, 32]. Meta-analysis of three studies [26–28] found little evidence of association between maternal smoking and JIA (pooled OR 0.75, 95% CI: 0.31, 1.81). Furthermore, one study [32] reported increased JIA risk associated with pre- and postnatal smoke exposure combined (adjusted OR 3.55, 95% CI: 1.38, 9.16). Two studies [27, 28] suggested that paternal (but not maternal or other relative) smoking inside the house is associated with decreased JIA risk (adjusted OR 0.26, 95% CI: 0.08, 0.81 and adjusted OR 0.64, 95% CI: 0.45, 0.92).

Infection-related factors

Nineteen studies examined the association between JIA and infection-related factors [21–24, 26, 28, 42, 46, 48–58] (Supplementary Fig. S1I, available at Rheumatology online). Most data (including all pathogen-specific data) is from unadjusted analyses; only 8/19 studies reported any adjusted estimates [21–24, 26, 28, 56, 57]. There was little evidence that specific bacterial pathogens were associated with JIA. Parvovirus B19 was inconsistently associated with increased JIA risk [49–52]. There was little evidence of association between JIA and other viruses. One study [26] reported increased JIA risk associated with all cause infections (adjusted OR 1.92, 95% CI: 1.69, 2.18), which was supported by adjusted and unadjusted data from other studies [46, 49]. Similarly, antibiotic use was positively associated with JIA (unadjusted OR 1.53, 95% CI: 1.26, 1.85) [42]. However, unadjusted data suggests this is independent of age or frequency of exposure [58]. There was little evidence of association between JIA and mebendazole [56], palivizumab [57] or human papilloma virus vaccination [21–24].

Environmental factors

Two studies [32, 59] examined factors related to the external environment (Supplementary Fig. S1J, available at Rheumatology online). Limited evidence suggests that higher maternal sunlight exposure during pregnancy is negatively associated with JIA [59]. Similarly, estimated childhood ultraviolet radiation exposure by quartile was also associated with decreased JIA risk in a dose-dependent manner (OR 0.19, 95% CI: 0.04, 0.85 for the highest quartile) [59]. With regard to pollutants, one study [32] reported that prenatal pollution exposure (adjusted OR 27.40, 95% CI: 6.85, 109.70) and exposure to second, but not third tertile, ozone in the first two years of life (adjusted OR 6.50, 95% CI: 2.15, 20.53 and adjusted OR 1.00, 95% CI: 0.54, 2.90, respectively) were risk factors for JIA.

Discussion

Summary of the evidence

The literature search strategy was designed to capture environmental factors in their broadest sense and identify all relevant studies regarding the association between these factors and JIA. A large number of articles were screened identifying 39 studies reporting 66 environmental factors for inclusion. Only eight environmental factors from ten studies were suitable for meta-analysis, highlighting the unmet need for replicated environmental research in JIA. Meta-analysis found strong evidence that CSD was associated with increased JIA risk whereas sibling status and maternal prenatal smoking appeared protective. There was limited evidence of increased JIA risk associated with post-term birth and SGA, and decreased JIA risk associated with maternal smoking, ≥3 siblings, birth weight (high or low) and preterm birth. No evidence of association between JIA and maternal age was found.

Of the 58 environmental factors not included in meta-analysis, some themes emerged. Consistent with sibling status, there was some evidence that increasing parity/number of prior births is protective of JIA whereas maternal fertility problems were associated with increased risk. However, data regarding number of siblings and birth order was conflicting. There was some evidence (largely from unadjusted data) of a positive association between JIA and both antibiotic exposure and early life infections but little evidence for specific pathogens. We found little evidence of association between JIA and maternal/child dietary factors, with the potential exception of fish consumption. Data regarding the association between JIA and breastfeeding status or duration of exclusive/total breastfeeding was highly conflicting. Low vitamin D levels have been causally implicated in multiple sclerosis risk [60]. However, only one study examined the association between vitamin D levels and JIA risk, finding no protective effect [29]. Other factors that influence vitamin D levels such as season of pregnancy/birth and maternal/offspring sunlight exposure showed conflicting findings.

Interpretation of findings

JIA is considered a complex disease, influenced by genetic and environmental factors. The environmental factors identified in this review support several hypotheses explaining the pathological process leading to autoimmunity in JIA. The hygiene hypothesis proposed that the presence of siblings and subsequent early life exposure to infections was protective of atopy and autoimmunity due to effects on the immune repertoire [61, 62]. Accordingly, meta-analysis found decreased JIA risk in association with sibling status. In contrast, infectious agents have been proposed to contribute to autoimmunity through several mechanisms such as molecular mimicry, epitope spreading and bystander activation [63]. However, we found no consistent evidence of specific pathogen risk factors for JIA. More recently, there is a growing interest in the contribution of the microbiome to human health. An estimated 22–36% of inter-person microbiome variation is attributed to environmental influences [64], with early life environmental factors such as mode of delivery and breastfeeding influencing the microbiome later in life [65]. We identified...
CSD as a risk factor for JIA. CSD is postulated to affect the microbiome in multiple ways, including lack of exposure to vaginal flora, which begins at rupture of membranes (indeed, Kristensen and Henriksen reported increased JIA risk associated with elective but not acute CSD [36]), or routine administration of prophylactic intrapartum antibiotics which can pass to the foetus [66]. Changes in the microbiome may provide a unifying hypothesis to explain the association between CSD and JIA plus the weaker evidence of an association between antibiotic use and early life infections and JIA. However, CSD may be associated with JIA independent of any effects on the microbiome or may be mediating another exposure rather than itself being a primary risk factor for JIA. We were unable to determine a robust association between JIA and other perinatal/maternal factors known influence mode of delivery (e.g. pre-/post-term delivery, high/low birth weight, increasing maternal age and conception via assisted reproductive technology) in this review; however, we cannot exclude other indications for CSD as the primary exposure influencing JIA risk. Furthermore, dissecting direction of association from observational data is challenging and it remains possible that any association between JIA and infectious agents/ the microbiome is in reverse; that JIA represents an end point of immune perturbation that also renders children more susceptible to infection and/or resultant exposure to antibiotics, or that active JIA disease/JIA treatments impact the microbiome.

Finally, environmental exposures have the potential to alter the epigenome and affect gene regulation [67]. Prenatal smoking has largely been associated with adverse offspring health and can alter immune responses [68], with altered DNA methylation a potential mediator [69]. Thus, our finding of a negative association with JIA was unanticipated. Explanations include specific effects of in utero smoke exposure on JIA risk or residual confounding, such as socioeconomic position or other measured/unmeasured confounders. However, the majority of studies of prenatal smoking did adjust for socioeconomic position. Furthermore, the effect of prenatal smoking on JIA risk is larger than for any other socioeconomic factor examined. Objective measures of prenatal smoking would be helpful to disentangle this association and limit potential reporting bias. Ultimately, the development of JIA is likely the result of complex and multifactorial immune interactions in genetically susceptible individuals, with many environmental factors making small but cumulatively important contributions to disease risk.

Limitations of individual studies

The studies included in this review have some inherent limitations. Many studies had small sample size, thus imprecise findings cannot be assumed to represent no effect. Several studies examined multiple environmental factors and/or undertook subgroup analyses but did not account for findings potentially resulting from chance due to multiple testing. Fourteen studies diagnosed JIA based on International Classification of Diseases coding rather than physician-defined criteria, which may lead to misclassification bias. Confounder adjustment was variable, with 15/39 studies performing no adjustment. Although JIA can occur throughout childhood, only 1/11 cohort studies followed patients up to age 16 years. Substantial (>5%), or absent reporting of, loss to follow-up affected 8/11 cohort studies, potentially biasing estimates. With regard to case-control studies, 10/28 did not use community control subjects, limiting the generalizability of the results. Additionally, half of the case-control studies did not report the case and control response rate; therefore, we cannot exclude non-response bias from these studies.

Strengths and limitations

Narrative reviews of environmental associations of JIA have recently been published [11, 12]. However, to our knowledge, this is the first study to systematically review environmental factors associated with JIA and attempt to quantify their effects. To its strength, this study conforms to PRISMA guidelines and was conducted in accordance with a pre-registered protocol [14]. We used a comprehensive and inclusive search strategy, composed with input from a literature searching specialist and implemented across multiple databases. To ensure the reliability of study selection, scoring and data extraction, all aspects involved a second, and where necessary a third, reviewer. The methodological quality of included studies was independently assessed using a validated scoring system. The included studies varied in quality; however, because JIA is rare we opted for inclusivity and no study was excluded based on quality assessment. Finally, to aid future research, in addition to the data reported in the main text, we have made our full dataset available.

The main limitation of this review is bias due to heterogeneity, which has arisen for several reasons. Firstly, the diagnostic criteria for JIA have evolved over the review period [3]. Secondly, individual studies varied in their inclusion/exclusion of specific JIA subtypes. Thirdly, because the review period spans 45 years, it is likely that social practices, and thus environment influences, have changed. Collectively, historic JIA cohorts may differ from those diagnosed using more recent criteria. However, two-thirds of studies were published in the past decade, and half within the past five years. Despite searching multiple databases and hand-searching bibliographies of excluded review articles, the breadth of this review means we may not have captured all relevant studies. Additionally, we excluded studies where we could not extract JIA-specific data from composite outcomes; such data may be informative. Due to resource constraints, only studies in English were included; however, we felt it unlikely that this led to omission of major relevant studies. We were unable to formally assess potential publication bias using funnel plots due to the small numbers of studies investigating each environmental factor. Bias may also result from
studies rarely adjusting for the same factors (if at all) and the different lengths of follow-up between studies. Environmental factors across studies were seldom identified, defined and/or measured in the same way, or could be transformed into comparable measures. This resulted in sufficient data to assess only eight factors using meta-analysis. Of these, three included only two studies. Accordingly, for most meta-analyses the pooled estimates were imprecise (encompassing weak evidence of both positive or negative effects) and should be interpreted with caution rather than taken as evidence of no effect. Several studies were excluded where the outcome was JIA course/severity rather than incidence. Whether environmental factors for disease course/severity overlap with those for incidence is an important research question but is outside the scope of this review. Finally, because this review includes only observational studies, the inevitable question remains as to whether our findings represent correlation or causation.

Implications of findings

Identifying robust risk or protective factors associated with JIA has enormous capability to alter patient counselling, aid risk stratification and inform future (causal) research. Furthermore, environmental factors may be modifiable with implications for population JIA risk reduction. The identification of risk (CSD) and protective (sibling status and prenatal smoking) factors associated with JIA necessitates further study into causality and mechanism, and the identification of other putative risk factors (e.g. antibiotics) highlights areas for research priority. The inability to pool the majority of environmental data underscores the need for research reproducibility and standardization of study design. Validating the findings of this review and identifying novel risk/protective factors will require further studies in large populations and likely require international collaboration and co-operation to align this work. Close consideration should be given to the measurement of and adjustment for confounders. Observational studies need to be integrated with mechanistic studies and other data modalities (such as genomic or microbiomic data) to attempt to delineate correlation from causation and improve our understanding of JIA aetiology.

Conclusions

This review highlights the plethora of environmental research undertaken in JIA over the last five decades and the challenges posed by using data from historical cohorts. The environmental factors identified here will assist in planning future studies to probe the extent of these associations and understand JIA aetiopathogenesis more broadly, which will ultimately translate into patient benefit.

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Data availability statement

All data underlying the results are from publicly available sources and are included within the article or uploaded as supplementary information. No additional source data are required.

Supplementary data

Supplementary data are available at Rheumatology online.

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