SUPPLEMENTARY APPENDIX

This appendix provides readers additional information about the study protocol, the literature search and results.

Supplement to: **“**Early-life Exposures and Risk of Inflammatory Bowel Disease: a Systematic Review and Meta-analysis **“**

SUPPLEMENTARY APPENDIX

Appendix A: Study Protocol and Literature Search

1. Study identification
2. Eligibility criteria
3. Study selection and data abstraction
4. Risk of bias and study quality
5. Qualitative and quantitative analysis
6. Literature search and results

Appendix B: Supplementary Tables

Supplementary Tables 1 a–j: Extracted data from studies on the association between early life exposures and inflammatory bowel disease

a. Maternal health and exposures during pregnancy
b. Perinatal factors
c. Birth month and related factors
d. Breastfeeding
e. Hygiene-related factors
f. Social factors
g. Immigration
h. Infections
i. Antibiotics and other medications
j. Passive exposure to tobacco smoke

Supplementary Table 2: Newcastle Ottawa Scale grading of all included studies

2a: Newcastle Ottawa Scale grading of case-control studies
2b: Newcastle Ottawa Scale grading of cohort studies

Appendix C: Supplementary Figures 1-33

APPENDIX A – STUDY PROTOCOL AND LITERATURE SEARCH

1. Study identification

We conducted the identification and retrieval of studies in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We developed and executed a comprehensive search strategy in collaboration with a medical librarian (CS). We searched Embase (Ovid), MEDLINE ALL (Ovid), and Global Health (Ovid) databases from the date of database inception though May 23, 2019. We repeated the search from January 2019 until July 14, 2020 to identify the more recent studies. We did not apply any language or date restriction at the initial search. We applied a filter for observational studies, adapted from the Observational Studies search filter developed by the Scottish Intercollegiate Guidelines Network (SIGN). The search was designed using a combination of free-text terms and subject headings specific to each database, EMBASE Emtree subject headings, MEDLINE Medical Subject Headings (MeSH), and Global Health CABI subject headings. We also searched references of all included studies as well as pertinent reviews. The full search query for all biomedical platforms is available in Appendix A. Search results were exported into the Covidence platform and de-duplicated. The review protocol was registered with PROSPERO (CRD42019134980). The following are deviations from the registered protocol: given that several important exposures were reported in smaller cohort and case-control studies, including exposures that cannot be ascertained in population-based administrative data, we extended the review beyond population-based studies. While we did not plan quantitative review at the outset due to heterogeneity overall, we added quantitative synthesis to the review in order to add further objectivity and granularity. We included all studies, including non-English at the initial search. Given the number of studies to be screened, and lack of relevant non-English studies, we excluded non-English studies during abstract screening.

2. Eligibility criteria

We included case-control and cohort studies that determined the association of early-life environmental risk factors with CD, UC or IBD overall. Early-life was defined as extending from prenatal period to 5 years of age. Based on prior literature review (MA, JS), we included all relevant nongenetic exposures and categorized them into (1) maternal exposures and health during pregnancy, (2) perinatal factors (3) birth month and related-factors (4) breastfeeding, (5) hygiene-related factors, (6) social factors, (7) immigration, (8) antibiotics and other medications, (9) offspring health, including infections, and (10) passive smoking. We excluded studies if the timing of the exposure was not clearly defined at ≤5 years of age. If studies reported data on both ≤5 and ≥5 years of age, we included only the former subset of patients. If multiple studies reported data from the same cohort, we included the most recent study, the one with the longest duration of follow-up, or the one with the largest sample size, in this order of priority. Studies published in a language other than English were excluded.

3. Study selection and data abstraction

Study selection and data extraction were performed by two of seven investigators (MA, JS, CFG, JA, SCS, TL and JT) independently using the Covidence platform. Any conflict during abstract or full-text screening was resolved by review of the pertinent study jointly, with an additional arbiter when needed. Data were extracted per the Cochrane Consumers and Communication Review Group's template. The following elements were recorded: the name and year of the study, the country and region where it was conducted, study period and design, exposure(s) and outcome(s) and estimates.

4. Risk of bias and study quality

The risk of bias and quality of studies were evaluated by two investigators independently, and jointly in case of discrepancy, using either the cohort or case-control studies instrument of the Newcastle-Ottawa Scale (NOS) (5). Studies

were evaluated in three domains: selection, comparability, and outcome, and were awarded a maximum of four, two or three points, respectively. A total score of seven or higher indicated a high-quality study.

5. Qualitative and quantitative analysis

We conducted random-effects meta-analyses to determine pooled estimates with 95% confidence intervals (CI) for homogenous exposures reported in ≥2 studies with comparable study design (cohort or case-control) and outcome (CD, UC or IBD). As recent meta-analyses have been conducted for exposures breastfeeding and mode of delivery, we deferred meta-analyzing data for these exposures. We report meta-analyses for the following exposures: maternal age at pregnancy, prenatal exposure to tobacco smoke, perinatal factors including preterm birth and birth weight, rural versus urban living, passive exposure to tobacco smoke during childhood, measles vaccination, otitis media and antibiotic exposure during the first year of life. Adjusted estimates were used when available. When relevant data were available from cohort studies, we calculated odds ratios in order to be able to pool with odds ratios from case-control studies. When feasible, case-control and cohort studies estimates were pooled and meta-regression performed to determine if there were differences based on study type. Heterogeneity was evaluated using the I^2 score. Meta-analyses were performed using the Comprehensive Meta-Analysis (version 2.0; Biostat, Englewood, NJ).
For exposure categories that were not analyzed quantitatively, we extracted relevant data and performed a systematic review.

6. Literature search and results

Literature search was run on Friday, May 24th 2019 and repeated on July 14, 2020.

Embase Classic+Embase 1947 to 2019 May 23
15351 references

1. exp migrant/
2. exp migration/
3. exp ethnology/
4. (emigra* or immigra* or migrant* or migrat* or ethnolog* or transient*).tw,kw.
5. or/1-4
6. exp antibiotic agent/
7. exp nonsteroid antiinflammatory agent/
8. oral contraception/ or exp oral contraceptive agent/ or hormonal contraception/
9. ((oral* or hormon*) adj3 contracept*).tw,kw.
10. (antibiotic* or penicillin* or cephalosporin* or tetracycline* or doxycycline* or minocycline* or fluoroquinolone* or macrolide* or sulfonamide* or metronidazole* or vancomycin*).tw,kw.
11. (nsaid* or ocp*).tw,kw.
12. ((nonsteroid* or non-steroid*) adj3 (antiinflammator* or anti-inflammator* or (anti adj2 inflammator*))).tw,kw.
13. or/6-12
14. exp helicobacter/
15. exp Campylobacter/
16. Helicobacter*.tw,kw.
17. Campylobacter*.tw,kw.
18. (H adj2 pylori).tw,kw.
19. cagA.tw,kw.
20. ((cytotoxin-associated or (cytotoxin adj2 associated)) adj4 A).tw,kw.

21. VacA.tw,kw.
22. (Vacuolating adj2 cytotoxin*).tw,kw.
23. exp disease elimination/
24. (eradication or elimination).tw,kw.
25. or/14-24
26. exp instrumental delivery/ or vaginal delivery/
27. (c?esarean* or c-section* or csection*).tw,kw.
28. (mode adj4 deliver*).tw,kw.
29. or/26-28
30. exp vaccine/
31. vaccin*.tw,kw.
32. appendectomy/
33. (appendectom* or appendicectom* or appendicitis).tw,kw.
34. appendix.tw,kw.
35. exp tonsillectomy/
36. tonsillectom*.tw,kw.
37. or/30-36
38. exp "physical activity, capacity and performance"/
39. exp sport/
40. (physical adj4 activit*).tw,kw.
41. (exercis* or sport*).tw,kw.
42. or/38-41
43. environmental exposure/
44. exp domestic animal/
45. exp farm animal/
46. urban rural difference/
47. urban hygiene/
48. rural hygiene/ or rural population/
49. urban population/
50. "crowding (area)"/
51. population density/ or population abundance/ or population size/
52. family size/
53. birth order/
54. environmental sanitation/ or exp microbial contamination/ or pollution control/ or pollution transport/ or exp water management/
55. refrigerator/
56. exp food preservation/
57. exp socioeconomics/
58. exp "pollution and pollution related phenomena"/
59. sun exposure/
60. exp ultraviolet radiation/
61. exp vitamin D/ or folic acid/
62. exp child abuse/
63. (environmental adj4 (factor* or exposure*)).tw,kw.
64. (protect* adj3 factor*).tw,kw.

65. (early adj3 life).tw,kw.
66. ((domestic* or farm*) adj4 animal*).tw,kw.
67. (pet or pets or dog* or cat or cats).tw,kw.
68. (famil* adj4 size*).tw,kw.
69. (birth adj4 order).tw,kw.
70. (sanitation or refrigerat* or pasteuriz* or pollut* or (food adj4 preserv*)).tw,kw.
71. (urban* or rural*).tw,kw.
72. socioeconomic*.tw,kw.
73. ((parent* adj3 occupation) or (social adj3 mixing)).tw,kw.
74. latitude/
75. (sun or ultraviolet* or UV or UVs or (vitamin adj4 D) or folate or (folic adj3 acid*) or latitude).tw,kw.
76. or/43-75
77. maternal stress/
78. exp maternal care/ or prenatal exposure/
79. maternal smoking/
80. ((maternal or mother* or pregnan* or postpartum or post-partum or prenatal* or pre-natal* or postnatal* or post-natal* or perinatal* or peri-natal* or peripartum or peri-partum or prepartum or pre-partum) adj5 (diet* or nutrition* or infection* or smok* or stress*)).tw,kw.
81. ((maternal or mother* or pregnan* or postpartum or post-partum or prenatal* or pre-natal* or postnatal* or post-natal* or perinatal* or peri-natal* or peripartum or peri-partum or prepartum or pre-partum) adj5 (risk adj4 factor*)).tw,kw.
82. or/77-81
83. exp child nutrition/
84. weaning/
85. (breastfeeding or breast-feeding or breastfed* or lactation or formula* or colostrum or (human adj3 milk*) or emulsifier*).tw,kw.
86. ((breast or bottle* or infant* or child*) adj4 feeding).tw,kw.
87. weaning.tw,kw.
88. or/83-87
89. exp parasite/
90. exp helminth/
91. exp hygiene/
92. hygiene hypothesis/
93. exp parasitosis/
94. exp smoking/
95. tobacco/
96. parasit*.tw,kw.
97. (helminth* or nematode* or tapeworm* or ascaria* or flatworm* or cestod* or trematod*).tw,kw.
98. hygien*.tw,kw.
99. infestation.tw,kw.
100. (smok* or tobacco*).tw,kw.
101. (diet* or nutrition* or food*).tw,kw.
102. or/89-101
103. exp child/
104. exp pediatrics/

105. (Infan* or newborn* or new-born* or perinat* or neonat* or baby* or babies or toddler* or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child* or schoolchild* or school-child*).mp.
106. (p?ediatric* or peadiatric* or prematur* or preterm*).mp.
107. school*.tw,kw.
108. or/103-107
109. 102 and 108
110. 5 or 13 or 25 or 29 or 37 or 42 or 76 or 82 or 88 or 109
111. exp inflammatory bowel disease/
112. (inflammatory adj4 bowel adj4 disease*).tw,kw.
113. ((ulcerative or ulcerous or mucosal or Idiopathic) adj3 (colitis or proctocolitis or colorectitis)).tw,kw.
114. (colitis adj3 (gravis or ulcerativa or ulcerosa)).tw,kw.
115. ((Crohn* or granulomatous) adj3 (disease* or enteritis or ileitis or ileitides or colitis or enterocolitis)).tw,kw.
116. ((regional or terminal) adj3 (enteritis or ileitis or ileitides or colitis or enterocolitis)).tw,kw.
117. (morbus adj3 crohn*).tw,kw.
118. or/111-117
119. Clinical study/
120. exp Case control study/
121. Family study/
122. Longitudinal study/
123. Retrospective study/
124. Prospective study/ or exp incidence/ or exp prevalence/
125. Randomized controlled trials/ or intervention study/
126. 124 not 125
127. Cohort analysis/
128. (Case control adj3 (study or studies)).mp.
129. (observational adj3 (study or studies)).mp.
130. (epidemiologic* adj3 (study or studies)).mp.
131. (cross sectional adj3 (study or studies)).mp.
132. (cohort or prospective or retrospective or population based or longitudinal).mp.
133. or/119-123,126-132
134. 110 and 118 and 133

Ovid MEDLINE (R) ALL 1946 to May 23, 2019

6315 references

1. "Transients and Migrants"/
2. exp Human Migration/
3. Ethnology/
4. (emigra* or immigra* or migrant* or migrat* or ethnolog* or transient*).tw,kf.
5. or/1-4
6. exp anti-bacterial agents/ or exp antifungal agents/
7. exp Anti-Inflammatory Agents, Non-Steroidal/
8. exp Contraception/
9. ((oral* or hormon*) adj3 contracept*).tw,kf.

10. (antibiotic* or penicillin* or cephalosporin* or tetracycline* or doxycycline* or minocycline* or fluoroquinolone* or macrolide* or sulfonamide* or metronidazole* or vancomycin*).tw,kf.
11. (nsaid* or ocp*).tw,kf.
12. ((nonsteroid* or non-steroid*) adj3 (antiinflammator* or anti-inflammator* or (anti adj2 inflammator*))).tw,kf.
13. or/6-12
14. exp Helicobacter/
15. exp Campylobacter/
16. Helicobacter*.tw,kf.
17. Campylobacter*.tw,kf.
18. (H adj2 pylori).tw,kf.
19. cagA.tw,kf.
20. ((cytotoxin-associated or (cytotoxin adj2 associated)) adj4 A).tw,kf.
21. VacA.tw,kf.
22. (Vacuolating adj2 cytotoxin*).tw,kf.
23. exp Disease Eradication/
24. (eradication or elimination).tw,kf.
25. or/14-24
26. exp Delivery, Obstetric/
27. (c?esarean* or c-section* or csection*).tw,kf.
28. (mode adj4 deliver*).tw,kf.
29. or/26-28
30. exp Vaccines/
31. vaccin*.tw,kf.
32. Appendectomy/
33. (appendectom* or appendicectom* or appendicitis).tw,kf.
34. appendix.tw,kf.
35. Tonsillectomy/
36. tonsillectom*.tw,kf.
37. or/30-36
38. exp Exercise/
39. exp Sports/
40. (physical adj4 activit*).tw,kf.
41. (exercis* or sport*).tw,kf.
42. or/38-41
43. exp Environmental Exposure/
44. exp Animals, Domestic/
45. exp Hygiene/
46. exp Population/
47. exp population health/ or maternal health/
48. population density/
49. Family Characteristics/
50. birth order/ or "social determinants of health"/
51. Sanitation/
52. Refrigeration/
53. exp Food Handling/

54. child health/ or infant health/ or maternal health/ or exp socioeconomic factors/
55. exp Environmental Pollution/
56. sunlight/
57. ultraviolet rays/
58. exp Vitamin D/ or exp Vitamin D Deficiency/ or exp Folic Acid/
59. exp Child Abuse/
60. (environmental adj4 (factor* or exposure*)).tw,kf.
61. (protect* adj3 factor*).tw,kf.
62. (early adj3 life).tw,kf.
63. ((domestic* or farm*) adj4 animal*).tw,kf.
64. (pet or pets or dog* or cat or cats).tw,kf.
65. (famil* adj4 size*).tw,kf.
66. (birth adj4 order).tw,kf.
67. (sanitation or refrigerat* or pasteuriz* or pollut* or (food adj4 preserv*)).tw,kf.
68. (urban* or rural*).tw,kf.
69. socioeconomic*.tw,kf.
70. ((parent* adj3 occupation) or (social adj3 mixing)).tw,kf.
71. (sun or ultraviolet* or UV or UVs or (vitamin adj4 D) or folate or (folic adj3 acid*) or latitude).tw,kf.
72. or/43-71
73. exp Maternal Behavior/
74. Prenatal Exposure Delayed Effects/
75. ((maternal or mother* or pregnan* or postpartum or post-partum or prenatal* or pre-natal* or postnatal* or post-natal* or perinatal* or peri-natal* or peripartum or peri-partum or prepartum or pre-partum) adj5 (diet* or nutrition* or infection* or smok* or stress*)).tw,kf.
76. ((maternal or mother* or pregnan* or postpartum or post-partum or prenatal* or pre-natal* or postnatal* or post-natal* or perinatal* or peri-natal* or peripartum or peri-partum or prepartum or pre-partum) adj5 (risk adj4 factor*)).tw,kf.
77. or/73-76
78. child nutritional physiological phenomena/ or exp infant nutritional physiological phenomena/ or exp maternal nutritional physiological phenomena/
79. exp Lactation/
80. (breastfeeding or breast-feeding or breastfed* or lactation or formula* or colostrum or (human adj3 milk*) or emulsifier*).tw,kf.
81. ((breast or bottle* or infant* or child*) adj4 feeding).tw,kf.
82. weaning.tw,kf.
83. or/78-82
84. exp helminths/
85. parasites/
86. exp hygiene/
87. hygiene hypothesis/
88. exp Parasitic Diseases/
89. exp "tobacco use"/
90. parasit*.tw,kf.
91. (helminth* or nematode* or tapeworm* or ascaria* or flatworm* or cestod* or trematod*).tw,kf.
92. hygien*.tw,kf.

93. infestation.tw,kf.
94. (smok* or tobacco*).tw,kf.
95. (diet* or nutrition* or food*).tw,kf.
96. or/84-95
97. exp child/ or exp infant/ or minors/
98. exp Pediatrics/
99. (Infan* or newborn* or new-born* or perinat* or neonat* or baby* or babies or toddler* or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child* or schoolchild* or school-child*).mp.
100. (p?ediatric* or peadiatric* or prematur* or preterm*).mp.
101. school*.tw,kf.
102. or/97-101
103. 96 and 102
104. 5 or 13 or 25 or 29 or 37 or 42 or 72 or 77 or 83 or 103
105. exp Inflammatory Bowel Diseases/
106. (inflammatory adj4 bowel adj4 disease*).tw,kf.
107. ((ulcerative or ulcerous or mucosal or Idiopathic) adj3 (colitis or proctocolitis or colorectitis)).tw,kf.
108. (colitis adj3 (gravis or ulcerativa or ulcerosa)).tw,kf.
109. ((Crohn* or granulomatous) adj3 (disease* or enteritis or ileitis or ileitides or colitis or enterocolitis)).tw,kf.
110. ((regional or terminal) adj3 (enteritis or ileitis or ileitides or colitis or enterocolitis)).tw,kf.
111. (morbus adj3 crohn*).tw,kf.
112. or/105-111
113. Clinical study/ or observational study/ or comparative study/ or Observational Studies as Topic/
114. controlled before-after studies/ or cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/
115. exp case-control studies/
116. epidemiologic studies/ or epidemiologic methods/
117. longitudinal studies/
118. retrospective studies/
119. Prospective Studies/ or incidence/ or prevalence/
120. randomized controlled trial/
121. 119 not 120
122. cohort studies/
123. (Case control adj3 (study or studies)).mp.
124. (observational adj3 (study or studies)).mp.
125. (epidemiologic* adj3 (study or studies)).mp.
126. (cross sectional adj3 (study or studies)).mp.
127. (cohort or prospective or retrospective or population based or longitudinal).mp.
128. or/113-118,121-127
129. 104 and 112 and 128

Global Health 1910 to 2019 Week 19

1396 references

1. exp migrants/
2. migration/

3. (emigra* or immigra* or migrant* or migrat* or ethnolog* or transient*).tw,kw.
4. or/1-3
5. exp antibiotics/
6. exp non-steroidal antiinflammatory agents/
7. exp oral contraceptives/ or exp contraceptives/
8. ((oral* or hormon*) adj3 contracept*).tw,kw.
9. (antibiotic* or penicillin* or cephalosporin* or tetracycline* or doxycycline* or minocycline* or fluoroquinolone* or macrolide* or sulfonamide* or metronidazole* or vancomycin*).tw,kw.
10. (nsaid* or ocp*).tw,kw.
11. ((nonsteroid* or non-steroid*) adj3 (antiinflammator* or anti-inflammator* or (anti adj2 inflammator*))).tw,kw.
12. or/5-11
13. exp helicobacter/
14. exp campylobacter/
15. Helicobacter*.tw,kw.
16. Campylobacter*.tw,kw.
17. (H adj2 pylori).tw,kw.
18. cagA.tw,kw.
19. ((cytotoxin-associated or (cytotoxin adj2 associated)) adj4 A).tw,kw.
20. VacA.tw,kw.
21. (Vacuolating adj2 cytotoxin*).tw,kw.
22. disease control/
23. (eradication or elimination).tw,kw.
24. or/13-23
25. caesarean section/ or exp birth/
26. (c?esarean* or c-section* or csection*).tw,kw.
27. (mode adj4 deliver*).tw,kw.
28. or/25-27
29. exp vaccines/
30. vaccin*.tw,kw.
31. (appendectom* or appendicectom* or appendicitis).tw,kw.
32. appendix.tw,kw.
33. tonsillectom*.tw,kw.
34. or/29-33
35. exp physical activity/
36. exp sport/
37. (physical adj4 activit*).tw,kw.
38. (exercis* or sport*).tw,kw.
39. or/35-38
40. exposure/
41. exp domestic animals/
42. pets/
43. exp hygiene/
44. rural population/
45. urban population/
46. population density/ or overpopulation/

47. exp crowding/
48. family size/
49. sanitation/ or food sanitation/ or sewage/ or waste disposal/
50. refrigerators/ or refrigeration/
51. exp food preservation/ or microbial contamination/ or food contamination/ or food hygiene/
52. socioeconomics/
53. exp pollution/ or pollution control/
54. solar radiation/
55. ultraviolet radiation/
56. exp vitamin d/ or folic acid/
57. child abuse/
58. (environmental adj4 (factor* or exposure*)).tw,kw.
59. (protect* adj3 factor*).tw,kw.
60. (early adj3 life).tw,kw.
61. ((domestic* or farm*) adj4 animal*).tw,kw.
62. (pet or pets or dog* or cat or cats).tw,kw.
63. (famil* adj4 size*).tw,kw.
64. (birth adj4 order).tw,kw.
65. (sanitation or refrigerat* or pasteuriz* or pollut* or (food adj4 preserv*)).tw,kw.
66. (urban* or rural*).tw,kw.
67. socioeconomic*.tw,kw.
68. ((parent* adj3 occupation) or (social adj3 mixing)).tw,kw.
69. latitude/
70. (sun or ultraviolet* or UV or UVs or (vitamin adj4 D) or folate or (folic adj3 acid*) or latitude).tw,kw.
71. or/40-70
72. lactating women/ or pregnant women/
73. exp prenatal period/
74. maternal nutrition/
75. ((maternal or mother* or pregnan* or postpartum or post-partum or prenatal* or pre-natal* or postnatal* or post-natal* or perinatal* or peri-natal* or peripartum or peri-partum or prepartum or pre-partum) adj5 (diet* or nutrition* or infection* or smok* or stress*)).tw,kw.
76. ((maternal or mother* or pregnan* or postpartum or post-partum or prenatal* or pre-natal* or postnatal* or post-natal* or perinatal* or peri-natal* or peripartum or peri-partum or prepartum or pre-partum) adj5 (risk adj4 factor*)).tw,kw.
77. or/72-76
78. exp child nutrition/ or child feeding/ or exp infant feeding/
79. weaning/
80. (breastfeeding or breast-feeding or breastfed* or lactation or formula* or colostrum or (human adj3 milk*) or emulsifier*).tw,kw.
81. ((breast or bottle* or infant* or child*) adj4 feeding).tw,kw.
82. weaning.tw,kw.
83. or/78-82
84. parasites/ or animal parasitic nematodes/
85. helminths/
86. toilets/

87. parasitoses/
88. tobacco smoking/
89. passive smoking/
90. parasit*.tw,kw.
91. (helminth* or nematode* or tapeworm* or ascaria* or flatworm* or cestod* or trematod*).tw,kw.
92. hygien*.tw,kw.
93. infestation.tw,kw.
94. (smok* or tobacco*).tw,kw.
95. (diet* or nutrition* or food*).tw,kw.
96. or/84-95
97. exp children/
98. paediatrics/
99. (Infan* or newborn* or new-born* or perinat* or neonat* or baby* or babies or toddler* or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child* or schoolchild* or school-child*).mp.
100. (p?ediatric* or peadiatric* or prematur* or preterm*).mp.
101. school*.tw,kw.
102. or/97-101
103. 96 and 102
104. 4 or 12 or 24 or 28 or 34 or 39 or 71 or 77 or 83 or 103
105. exp inflammatory bowel diseases/
106. (inflammatory adj4 bowel adj4 disease*).tw,kw.
107. ((ulcerative or ulcerous or mucosal or Idiopathic) adj3 (colitis or proctocolitis or colorectitis)).tw,kw.
108. (colitis adj3 (gravis or ulcerativa or ulcerosa)).tw,kw.
109. ((Crohn* or granulomatous) adj3 (disease* or enteritis or ileitis or ileitides or colitis or enterocolitis)).tw,kw.
110. ((regional or terminal) adj3 (enteritis or ileitis or ileitides or colitis or enterocolitis)).tw,kw.
111. (morbus adj3 crohn*).tw,kw.
112. or/105-111
113. case studies/
114. case-control studies/
115. longitudinal studies/
116. retrospective studies/
117. epidemiology/ or disease prevalence/ or epidemiological surveys/
118. cohort studies/
119. (Case control adj3 (study or studies)).mp.
120. (observational adj3 (study or studies)).mp.
121. (epidemiologic* adj3 (study or studies)).mp.
122. (cross sectional adj3 (study or studies)).mp.
123. (cohort or prospective or retrospective or population based or longitudinal or prevalence or incidence).mp.
124. or/113-123
125. 104 and 112 and 124

APPENDIX B: Supplementary Tables

Supplementary Tables 1 a–j: Extracted data from studies on the association between early life exposures and inflammatory bowel disease

a. Maternal health and exposures during pregnancy
b. Perinatal factors
c. Birth month and related factors
d. Breastfeeding
e. Hygiene-related factors
f. Social factors
g. Immigration
h. Antibiotics and other medications
i. Offspring health and infections
j. Passive exposure to tobacco smoke

Effect estimates	Symbol
OR	*
aOR	**
HR	†
aHR	††
IRR	‡
aIRR	‡‡
MD	¶
RR	§
aRR	§§
SIR	#

Supplementary Table 2: Newcastle Ottawa Scale grading of all included studies
2a: Newcastle Ottawa Scale grading of all included case-control studies
2b: Newcastle Ottawa Scale grading of all included cohort studies

Study Type	Study	Study location	Study Time Period	Exposure Description	Total sample size (n)	Outcome	Period of exposure	Effect estimate value	Confidence interval (specify of different from 95% CI)	Comments
Cohort Studies										
	Aspberg, S. et al. 2006	Sweden	1987-2000	Maternal smoking during pregnancy (any compared with none)	274390	CD	Pregnancy	0.73**	0.58-0.94	Adjusting variables not reported
					274390	UC	Pregnancy	0.7**	0.56-0.86	
				Maternal age (25-34 vs < 25)	1250224	IBD	Perinatal	0.87**	0.69-1.10	
					1249949	CD	Perinatal	0.8**	0.63-1.01	
					1250078	UC	Perinatal	0.77**	0.63-0.94	
				Maternal age (25-34 vs > 35)	1110822	IBD	Perinatal	0.98**	0.71-1.32	
					1110583	CD	Perinatal	1.03**	0.77-1.39	
					1110689	UC	Perinatal	0.86**	0.65-1.13	
				Preeclampsia	1436235	IBD	Perinatal	0.85**	0.42-1.72	
	Blomster, T.M. et al. 2014	Finland	1966	Smoking during pregnancy	6685	IBD	Pregnancy	1.7§	1.2-2.5	Unadjusted estimates reported
				Antibiotics during pregnancy	6685	IBD	Pregnancy	1.6§	1-2.4	
	Burnett, D. et al. 2020	Canada	1988-2014	Maternal age (clinical cohort)	262705	IBD	Perinatal	Not Significant		
				Maternal age (administrative cohort)	42906	IBD	Perinatal	Not Significant		
	Elten, M. et al. 2020	Canada	April 1st, 1991 to March 31st, 2014	Maternal age	2218789	IBD	Perinatal	Not Significant		
				Air pollutant, nitrogen dioxide	2218789	IBD	Pregnancy	1††	0.96-1.03	Adjusted for sex, maternal IBD, rural/urban area of residence at birth, median neighborhood household income
				Air pollutant, fine particulate matter	2218789	IBD	Pregnancy	0.91††	0.79-1.04	
				Air pollutant, ozone	2218789	IBD	Pregnancy	0.9††	0.73-1.10	
				Air pollutant, oxidant capacity	2218789	IBD	Prenatal	1.12††	0.79-1.59	
	Greenbaum, S. et al. 2018	Israel	1991-2014	Maternal smoking during pregnancy	242342	IBD	Pregnancy	1.5*	1.2-3.9	Unadjusted estimates reported
	Konijeti, G. et al. 2013	USA	1976-2008	Maternal age (20-29 vs 30-39)	117976	CD	Perinatal	0.62††	0.44-0.87	Adjusted for age, BMI, tobacco use, regular use of oral contraceptives, exposure to parental smoking, birth weight, history of being breast fed, and being born preterm
				Maternal age (20-29 vs > 40)	117976	CD	Perinatal	0.87††	0.43-1.75	
	Lange, A. et al. 2014	Denmark	1995-2009	Maternal smoking	979039	CD	Infancy	0.8††	0.6-1.2	Adjusting variables not reported
	Ortqvist, A.K. et al. 2017	Sweden	2006-2013	Antibiotics during pregnancy	827239	IBD	Pregnancy	1.93††	1.06-3.5	Adjusted for maternal and paternal history of IBD, parental education, maternal and paternal country of birth, and mode of delivery
					827239	CD	Pregnancy	2.48††	1.01-6.08	
					827239	UC	Pregnancy	1.25††	0.47-3.26	
	Ponsonby, A.L. et al. 2009	Australia	1983-1998	Maternal age (< 25 vs 26-28)	513740	CD	Perinatal	1.29†	0.89-1.85	Adjusted for sex, abormality, interventional birth, urban, married, SES, maternal age and year of birth
				Maternal age (< 25 vs 29-32)	565218	CD	Perinatal	1.48†	1.05-2.08	
				Maternal age (< 25 vs > 33)	495539	CD	Perinatal	1.41†	0.97-2.05	
				Past spontaneous abortion (No vs Yes)	998655	CD	Perinatal	1.03†	0.77-1.39	
Case-Control Studies										
	Bernstein, C.N. et al. 2017	Canada	1984-2010	Maternal infection within 9 mo before delivery	12159	IBD	Pregnancy	0.96**	0.84-1.09	Adjusted for urban vs rural residence, SES, age, and sex
				Maternal infection within 30d before delivery	12159	IBD	Pregnancy	0.97**	0.82-1.14	
				Maternal infection peripartum	12159	IBD	Perinatal	0.86**	0.68-1.09	
	Canova, C. et al. 2020	Italy	1989-2012	Maternal age (25-29 vs < 25)	829	IBD	Perinatal	0.97**	0.57-1.63	Adjusted for sex, year of birth, season of birth, having older sibilings, number of births, birth weight, gestational age, Apgar score at 1 minute, maternal age and mother's education
				Maternal age (25-29 vs 30-34)	1247	IBD	Perinatal	0.76**	0.51-1.14	
				Maternal age (25-29 vs 35-39)	906	IBD	Perinatal	0.74**	0.43-1.27	
				Maternal age (25-29 vs >= 40)	655	IBD	Perinatal	1.55**	0.61-3.91	
	Ekbom, A. et al. 1990	Sweden	1924-1957	Maternal age	771	IBD	Perinatal	0.4¶	-1,8	Unadjusted estimates reported
					771	CD	Perinatal	0.7¶	-2,8	
					771	UC	Perinatal	0.3¶	-2,4	
	Gruber, M. et al. 1996	USA	Not Reported	Mother smoking during pregnancy	144	CD	Pregnancy	0.604*	0.29-1.3	Unadjusted estimates reported
	Han, D.Y. et al. 2010	New Zealand	Not Reported	Maternal smoking	727	CD	Pregnancy	1.44*	0.97-2.15	Unadjusted estimates reported
				Mother takes any regular medication during her pregnancy	851	CD	Pregnancy	2.02*	1.09-3.75	
	Holmes, E.A. et al. 2019	Australia	2010-2013	Mother smoking when pregnant	495	IBD	Pregnancy	Not Reported		
	Hutfless, S. et al. 2012	USA	1996-2006	Gestational hypertension, preeclampsia, or eclampsia	2825	IBD	Pregnancy	1.7*	1-2.8	Adjusted for sex, race, maternal age, maternal smoking, maternal diabetes, known or suspected fetal abnormality, maternal IBD, maternal infection, and placental or amniotic problems
				Placental or amniotic problems	2825	IBD	Pregnancy	1*	0.7-1.5	Adjusted for sex, race, maternal age, maternal smoking, maternal diabetes, known or suspected fetal abnormality, maternal IBD, maternal infection, and gestational hypertension
				Maternal infection, inpatient or outpatient visit	2825	IBD	Pregnancy	0.9*	0.5-1.5	Adjusted for sex, race, maternal age, maternal smoking, maternal diabetes, known or suspected fetal abnormality, maternal IBD, placental or amniotic problems, and gestational hypertension
	Mahid, S.S. et al. 2007	USA	Not Reported	Prenatal smoke exposure	495	CD	Perinatal	1.72**	1.1-2.71	Adjusted for age
					419	UC	Perinatal	1.53**	0.93-2.49	
	Malmborg, P. et al. 2012	Sweden	1973-2006	Maternal UTI during pregnancy	16975	CD	Pregnancy	1.27*	1.01-1.59	Unadjusted estimates reported
	Radon, K. et al. 2007	Germany	March 2006 to August 2006	Smoking during pregnancy	2229	IBD	Pregnancy	Not reported		
					2229	CD	Pregnancy	0.5**	0.3-0.8	Adjusted for age, gender, region, parental education, maternal and paternal history of IBD, nutrition other than breast milk at <5mo, birth weight ≤ 2500 g, ≥ 2 older siblings, rhinitis, and living in urban area
					2229	UC	Pregnancy	0.9**	0.6-1.3	
	Russell, R.K. et al. 2005	Scotland	Not Reported	Maternal smoking during pregnancy	124	IBD	Pregnancy	4.46*	1.16-17.1	Unadjusted estimates reported
	Sonntag, B. et al. 2007	Germany	2003-2004	Disease During Pregnancy	1834	CD	Pregnancy	1.519**	0.905-2.551	Adjusted for disease during 1st year, preterm birth, maternal IBD, appendectomy, ever smoking, sex
					1548	UC	Pregnancy	1.267**	0.735-2.183	
	Strisciuglio, C. et al. 2017	Italy	2000-2014	Diseases during pregnancy (Risk of premature delivery, hormonal treatment, diabetes, hypertension, infections)	467	IBD	Pregnancy	Not reported		
	Thompson, N.P. et al. 2000	UK	1946-1958	Infection during pregnancy	287	CD	Pregnancy	1.27*	0.26-5.31	Unadjusted estimates reported
					287	UC	Pregnancy	0.84*	0.12-4.35	
	Thorsen, S.U. et al. 2016	Denmark	1981–2004	Maternal age at delivery 25–35 compared with <25 years	384	IBD	Perinatal	1.27**	0.89-1.80	Adjusted for 25(OH)D, gender, ethnicity, birth weight (categorical), gestational age (categorical) and mother's age (categorical)
				Maternal age at delivery ≥35 compared with <25 years	384	IBD	Perinatal	1.29**	0.71-2.36	
	van der Sloot, K. et al. 2020	Netherlands	Not Reported	Prenatal smoking	1671	CD	Pregnancy	1.89*	1.38-2.59	Adjusted for age, sex, and history of smoking
					1669	UC	Pregnancy	1.62*	1.17-2.24	
	Van Limbergen, J.E. et al. 2009	Scotland	Not Reported	Parental smoking during pregnancy, at birth	252	IBD	Neonatal	Not reported		
	Velosa, M. et al. 2019	Israel	1964-1976	Mother's age at the time of delivery	1744	IBD	Perinatal	Not reported		
	Yoles, I. et al. 2018	Israel	1991-2014	Maternal Group B Streptococcus (GBS) colonization	195457	IBD	Pregnancy	1.29†	1.03-1.6	Adjusting variables not reported
	Yu, I. et al. 2016	Ireland	2012-2015	Maternal smoking during pregnancy	209	CD	Pregnancy	Not reported		
					187	UC	Pregnancy	Not reported		

Study Type	Study	Study location	Study Time Period	Exposure Description	Total sample size (n)	Outcome	Period of exposure (prenatal/ perinatal/ infancy/2-5 years of age)	Effect Estimate value	Confidence Interval (specify if different from 95% CI)	Comments
Cohort Studies										
	Andersen, V. et al. 2013	Denmark	1977-2009	C-section	2672708	IBD	Perinatal	1.07*	1.02-1.12	Adjusted for birth order, maternal age, gestational age, SGA, maternal IBD, paternal IBD, hospital admissions due to infection, maternal smoking, antibiotic treatment during pregnancy
					1984758	CD	Perinatal	1.1‡‡	0.99-1.22	
					1984758	UC	Perinatal	1.18‡‡	1.08-1.28	
				C-section (boys)	1984758	IBD	Perinatal	1.26‡‡	1.15-1.37	
				C-section (girls)	1984758	IBD	Perinatal	1.06‡‡	0.97-1.15	
	Aspberg, S. et al. 2006	Sweden	1987-2000	Birth weight (< 2500g vs > 2500g)	1479216	IBD	Perinatal	1.05**	0.65-1.72	Adjusting variables not reported
				Prematurity	1479216	IBD	Perinatal	1.17**	0.80-1.72	
	Bager, P. et al. 2012	Denmark	1995–2008	C-section	2098039	IBD	Perinatal	1.14‡‡	1.06-1.22	Adjusted for age, calendar-year, sex, birth weight, birth order, and country of birth
	Black, M. et al. 2015	Scotland	1993-2007	C-section	40145	IBD	Perinatal	0.82**	0.43-1.56	Adjusting variables not reported
	Black, M. et al. 2015	Scotland	1993-2007	C-section	265272	IBD	Perinatal	1.3††	0.62-2.73	Adjusted for maternal age, gestation at birth, maternal Carstairs decile, maternal smoking status, birth weight, year of delivery, male infant, and breastfeeding at 6 weeks
	Burnett, D. et al. 2017	Canada	1988-2014	C-section	262729	IBD	Perinatal	1.07‡‡	0.82-1.42	Adjusted for maternal age, parity, area-level income, rural residence, smoking, weight status, and birth weight for gestational age
	Burnett, D. et al. 2020	Canada	1988-2014	C-section (clinical cohort)	262705	IBD	Perinatal	1‡‡	0.76-1.31	Adjusted for maternal pre-pregnancy weight status, maternal age at birth, parity, Quintile of Annual income per person equivalent (QAIPPE), area of residence, and smoking during pregnancy
				C-section (administrative cohort)	42906	IBD	Perinatal	1.11‡‡	0.77-1.59	
				C-section (clinical cohort)	262705	CD	Perinatal	1.07‡‡	0.77-1.48	
				C-section (administrative cohort)	42906	CD	Perinatal	Not Reported		
				C-section (clinical cohort)	262705	UC	Perinatal	0.88‡‡	0.54-1.43	Adjusted for maternal pre-pregnancy weight status, maternal age at birth, parity, Quintile of Annual income per person equivalent (QAIPPE), area of residence, and smoking during pregnancy
				C-section (administrative cohort)	42906	UC	Perinatal	Not Reported		
				Birth weight (small for gestational age) - clinical cohort	262705	IBD	Perinatal	Not Significant		
				Birth weight (small for gestational age) -administrative cohort	42906	IBD	Perinatal	Not Significant		
				Birth weight (large for gestational age) - clinical cohort	262705	IBD	Perinatal	Not Significant		
				Birth weight (large for gestational age) - administrative cohort	42906	IBD	Perinatal	Not Significant		
	Elten, M. et al. 2020	Canada	April 1st, 1991 to March 31st, 2014	Birth weight	2218789	IBD	Perinatal	Not Significant		
				Prematurity	2218789	IBD	Perinatal	Not Significant		
	Khalili, H. et al. 2013	USA	1991- June 1, 2007 (NHSII) and 1992- June 1, 2008 (NHSI)	Birth weight (2.3-3.175 vs < 2.26)	143681	CD	Perinatal	1.29‡‡	0.79-2.11	Adjusted for age (months), cohort (NHSI vs. NHSII), BMI (<20, 20–24.9, 25–29.9, ≥ 30 kg/m2), smoking (never, past, current), history of diabetes in the mother (yes, no), maternal smoking during pregnancy (yes, no, unknown), ever use of oral contraceptives (yes, no), prematurity (yes, no), and having been breastfed (yes, no).
					143681	UC	Perinatal	0.91‡‡	0.55-1.49	
				Birth weight (2.3-3.175 vs 3.2-4.54)	143681	CD	Perinatal	1‡‡	0.74-1.34	
					143681	UC	Perinatal	0.98‡‡	0.75-1.27	
				Birth weight (2.3-3.175 vs > 4.54)	143681	CD	Perinatal	1.06‡‡	0.71-1.58	
					143681	UC	Perinatal	1.02‡‡	0.71-1.37	
				Prematurity	143681	CD	Perinatal	0.69‡‡	0.37-1.29	
					143681	UC	Perinatal	0.81‡‡	0.46-1.43	
	Konijeti, G. et al. 2013	USA	1976-2008	Paternal age	117976	CD	Perinatal	Not Significant		
	Lange, A. et al. 2014	Denmark	1995-2009	C-section	979 039	CD	Perinatal	1.3‡	0.9-1.8	Unadjusted estimates reported
				Prematurity	972 188	CD	Perinatal	1.2‡	0.7-2.1	
	Ponsonby, A.L. et al. 2009	Australia	1983–1998	Elective C-section	765 840	CD	Perinatal	1.67†	1.17-2.39	Adjusted for sex, abormality, interventional birth, urban, married, SES, maternal age, and year of birth
				Birth weight (< 1500 g vs 2500-3999)	837 353	CD	Perinatal	0.65††	0.16-2.62	
				Birth weight (1500-2499g vs 2500-3999)	875 767	CD	Perinatal	0.68††	0.36-1.28	
				Birth weight (> 4000g vs 2500-3999)	942 058	CD	Perinatal	0.87††	0.59-1.28	
				Single vs multiple birth	998877	CD	Perinatal	0.46††	0.17-1.22	
				Prematurity (Gestational age > 37w vs < 27w)	934633	CD	Perinatal	0.93††	0.13-6.73	
				Prematurity (Gestational age > 37w vs 28-36w)	989685	CD	Perinatal	0.88††	0.53-1.46	
				Apgar score (10 vs 9)	917739	CD	Perinatal	0.93††	0.72-1.19	
				Apgar score (10 vs 5-8)	539147	CD	Perinatal	1.04††	0.67-1.62	
				Apgar score (10 vs 0-4)	469091	CD	Perinatal	0.64††	0.09-4.58	
	Steiner, N. et al. 2019	Southern Israel	1991- 2014	Birth weight (SGA < 5% centile for gestational age)	215804	IBD	Perinatal	1.23**	1.14-1.33	Adjusted for maternal age
Case-Control Studies										
	Ananthakrishanan, A.N. et al. 2015	Boston	Not Reported	C-section	895	IBD	Perinatal	Not Significant		
	Baron, S. et al. 2005	Northern France	1988-1997	Disease during pregnancy and risk of prematurity	444	CD	Perinatal	Not Reported		
					120	UC	Perinatal	4.67*	1.3-16.1	Unadjusted estimates reported
	Bernstein, C.N. et al. 2016	Canada	1984-2010	C-section	12159	IBD	Perinatal	1.05**	0.89-1.24	Adjusted for urban vs rural residence and socioeconomic status (quintiles)
	Bernstein, C.N. et al. 2019	Canada	1970-2010	C-section	6824	IBD	Perinatal	1.06*	0.86-1.32	Unadjusted estimates reported
				Birth weight	6824	IBD	Perinatal	1*	1-1	
				Apgar score 1 min (> 7 vs < 7)	6824	IBD	Perinatal	1.09*	0.86-1.39	
					6824	CD	Perinatal	1.42*	1.02-1.96	
					6824	UC	Perinatal	0.78*	0.55-1.11	
				Apgar 5 min (> 7 vs < 7)	6824	IBD	Perinatal	1.07*	0.49-2.33	
					6824	CD	Perinatal	1.33*	0.38-4.61	
					6824	UC	Perinatal	1.04*	0.37-2.89	
				Gestational age	6824	IBD	Perinatal	1.004*	0.95-1.06	
					6824	CD	Perinatal	1.01*	0.94-1.08	
					6824	UC	Perinatal	0.99*	0.91-1.08	
	Canova, C. et al. 2020	Italy	1989-2012	Birth weight (> 2500 vs < 2500)	1804	IBD	Perinatal	1.12**	0.42-3.00	Adjusted for sex, year of birth, season of birth, having older sibiling, number of births, birth weight, gestational age, Apgar score at 1 minute, maternal age, and mother's education
				Single vs multiple birth	1804	IBD	Perinatal	1.44**	0.49-4.19	
				Gestational age (> 36 vs < 35)	1798	IBD	Perinatal	1.26**	0.40-4.03	
				Apgar score (>= 7 vs < 7)	1712	IBD	Perinatal	0.96**	0.47-1.96	
	Decker, E. et al. 2010	Germany	May 2008 and May 2009	C-section	912	UC	Perinatal	0.87*	0.55-1.38	Unadjusted estimates reported
					1117	CD	Perinatal	1.14*	0.83-1.58	
	Doyle, J.B. et al. 2017	Nothern Ireland	1971-1986	C-section	67173	IBD	Perinatal	0.85*	0.53-1.38	
	Ekbom, A. et al. 1990	Sweden	1924-1957	Birth weight	771	IBD	Perinatal	4§	-69-78	Unadjusted estimates reported
					771	CD	Perinatal	19§	-99-138	
					771	UC	Perinatal	-4§	-98-90	
				Prematurity	771	IBD	Perinatal	0.5*	0.2-1.2	
					771	CD	Perinatal	0.7*	0.2-3.0	
					771	UC	Perinatal	0.4*	0.1-1.3	
	Gilat, T. et al. 1987	9 countries (Europe, USA)	Not Reported	Birth weight	1497	IBD	Perinatal	Not Reported		
				Prematurity	1497	IBD	Perinatal	Not Reported		
	Hutfless, S. et al. 2012	Nothern California	1996-2006	C-section	3269	IBD	Perinatal	1.1**	0.7-1.6	Adjusted for race, sex, maternal age, gestational hypertension, placental or amniotic problems, birth weight, gestational age
					3269	CD	Perinatal	1.3**	0.7-2.4	
					3269	UC	Perinatal	0.7**	0.4-1.4	
				Birth weight (< 2500g)	3269	IBD	Perinatal	1.6**	0.7-10.4	
					3269	CD	Perinatal	2.7**	0.7-1.6	
					3269	UC	Perinatal	1.6**	0.5-5.1	
				Gestational age (> 37 vs < 36w)	3269	IBD	Perinatal	0.6**	0.3-1.5	
					3269	CD	Perinatal	0.4**	0.1-1.6	
					3269	UC	Perinatal	0.6**	0.2-2.2	
	Klein, I. et al. 1998	Israel	1992-1993	Birth weight	199	CD	Perinatal	Not Significant		
					177	UC	Perinatal	Not Significant		
	Levy, L.C. et al. 2012	US cohort	Not Reported	C-section	1458	IBD	Perinatal	Not Reported		
	Malmborg, P. et al. 2012	Sweden	1973–2006	C-section	16975	CD	Perinatal	1.14**	0.97-1.34	Adjusted for maternal infection and socioeconomic index
				Birth weight (< 1500 g)	16368	CD	Perinatal	Not Reported		
				Birth weight (1500-2499g)	16863	CD	Perinatal	Not Reported		
	Radon, K. et al. 2007	Germany	March 2006 and August 2006	Birth weight (< 2500g)	1925	CD	Perinatal	0.5**	0.4-0.7	Adjusted for age, gender, region, and parental education and mutually adjusted for parental IBD, male gender, nutrition other than breast milk < 5 mo, maternal smoking, ≥ 2 siblings, rhinitis, living in urban area
					1785	UC	Perinatal	0.5**	0.3-0.8	
	Sonntag, B. et al. 2007	Germany	January 2003 and March 2004	C-section	1974	CD	Perinatal	1.45*	0.96-2.19	Unadjusted estimates reported
					1641	UC	Perinatal	1.31*	0.83-2.01	
				Birth weight	1974	CD	Perinatal	1.52*	1.12-2.07	
					1641	UC	Perinatal	1.38*	0.99-1.92	
				Preterm birth	1974	CD	Perinatal	1.059**	0.724-1.547	Adjusted for disease during 1st year, pregnancy diseases, maternal IBD, appendectomy, ever smoking, sex
					1641	UC	Perinatal	0.941*	0.642-1.379	
	Thompson, N.P. et al. 1995	England	1950-1968	Birth weight	2522	IBD	Perinatal	Not Significant		
				Prematurity	2522	CD	Perinatal	1.1*	0.95-1.48	Unadjusted estimates reported
					2522	UC	Perinatal	1.35*	0.98-1.86	
	Thorsen, S.U. et al. 2016	Denmark	1981–2004	Birth weight <2500 compared with 2500–4499 g	384	IBD	Perinatal	1.21**	0.59-2.48	Adjusted for 25(OH)D, gender, ethnicity, birth weight (categorical), gestational age (categorical) and mother's age (categorical)
				Birth weight ≥4500 compared with 2500–4499 g	384	IBD	Perinatal	0.42**	0.13-1.41	
				Gestational age <37 compared with 37–41.99 weeks	384	IBD	Perinatal	0.84**	0.35-2.01	
				Gestational age ≥42 compared with 37–41.99 weeks	384	IBD	Perinatal	1.37**	0.82-2.31	
	van der Sloot, K. et al. 2020	Netherlands	Not Reported	C-section	1671	CD	Perinatal	0.64*	0.32-1.32	Unadjusted estimates reported
					1669	UC	Perinatal	1.01*	0.53-1.92	
				Birth weight (low vs medium)	1671	CD	Perinatal	0.98*	0.67-1.45	
					1669	UC	Perinatal	1.06*	0.73-1.54	
				Birth weight (low vs high)	1671	CD	Perinatal	0.77*	0.52-1.15	
					1669	UC	Perinatal	0.82*	0.55-1.20	
	Velosa, M. et al. 2019	Israel	1964-1976	C-section	1744	IBD	Perinatal	Not Reported		
				Birth weight	1744	IBD	Perinatal	Not Reported		

Study type	Study	Study location	Study Time Period	Exposure Description	Total sample size (n)	Outcome	Period of exposure	Effect estimate value	Confidence interval (specify of different from 95% CI)	Comments
Cohort studies										
	Chowers, Y et al. 2004	Israel	Not Reported	Month of birth January	844	CD	Birth	2[#]	1.37-2.4	Unadjusted estimates reported
					844	UC	Birth	1.21[#]	0.76-1.65	Unadjusted estimates reported
				Month of birth February	844	CD	Birth	1.36[#]	1.11-2.13	Unadjusted estimates reported
					844	UC	Birth	0.69[#]	0.33-1.05	Unadjusted estimates reported
				Month of birth April	844	CD	Birth	0.61[#]	0.24-0.82	Unadjusted estimates reported
					844	UC	Birth	1.12[#]	0.66-1.58	Unadjusted estimates reported
				Month of birth May	844	CD	Birth	0.68[#]	0.30-0.90	Unadjusted estimates reported
					844	UC	Birth	1.37[#]	0.87-1.87	Unadjusted estimates reported
				Month of birth November	844	CD	Birth	1.23[#]	1.04-1.98	Unadjusted estimates reported
					844	UC	Birth	0.9[#]	0.50-1.29	Unadjusted estimates reported
				Month of birth December	844	CD	Birth	1.18[#]	1.07-1.99	Unadjusted estimates reported
					844	UC	Birth	1.02[#]	0.61-1.42	Unadjusted estimates reported
	Khalili, H. et al. 2012	USA	IBD diagnosis between June 1976 to June 2002 (NHS I), between June 1989 to June 2003 in NHS II	Residence at Southern latitude (south of 37º N) compared with Northern (north of north of 41- 42º)	844	CD	Birth	1.02[$$]	0.66-1.58	Adjusted for age (Month), body mass index (<21, 21e24.9, 25e29.9, $30 kg/m2), ancestry (Southern European, Scandinavian, other Caucasian, non-white), oral contraceptive use (never, past, current), hormonal replacement therapy (never, past, current, premenopause), smoking (never, past, present)
					844	UC	Birth	1.02[$$]	0.80-1.29	Adjusted for age (Month), body mass index (<21, 21e24.9, 25e29.9, $30 kg/m2), ancestry (Southern European, Scandinavian, other Caucasian, non-white), oral contraceptive use (never, past, current), hormonal replacement therapy (never, past, current, premenopause), smoking (never, past, present)
				Residence at Middle latitudes compared with Northern latitudes	844	CD	Birth	0.91[$$]	0.70-1.19	Adjusted for age (Month), body mass index (<21, 21e24.9, 25e29.9, $30 kg/m2), ancestry (Southern European, Scandinavian, other Caucasian, non-white), oral contraceptive use (never, past, current, premenopause), smoking (never, past, present)
					844	UC	Birth	0.69[$$]	0.44-1.07	Adjusted for age (Month), body mass index (<21, 21e24.9, 25e29.9, $30 kg/m2), ancestry (Southern European, Scandinavian, other Caucasian, non-white), oral contraceptive use (never, past, current, premenopause), smoking (never, past, present)
	Sonnenberg, A. et al. 2009	England	Born between April 1997 and March 2006	Seasonality/Month of birth	54927510	IBD	Birth	Not reported		
					54927510	CD	Birth	Not reported		
					54927510	UC	Birth	Not reported		
	Ponsonby A.L. et al. 2009	Victoria, Australia	Born between 1983–1998	Spring birth compared with others	253500	CD	Birth	0.99[††]	0.75-1.30	Adjusting variables not reported
	Card T.R. et al. 2002	England	1978-1998	Month of birth October	15710000	IBD	Birth	Not significant		
					15710000	CD	birth	Not significant		
					15710000	UC	Birth	Not significant		
	Ekbom, A. et al. 1991	Sweden	1924-1957	Spring Birth compared with others	610655	CD	Birth	Not reported		
					610655	UC	Birth	Not reported		
Case-control studies										
	Shaw, S.Y. et al. 2014	Canada	1984 to 2010	Season of birth: January-March	119 786	IBD	Birth	0.98[*]	0.93-1.02	Unadjusted estimates reported
				Season of birth: April-June	119 786	IBD	Birth	1.07[*]	1.02-1.12	Unadjusted estimates reported
				Season of birth: July-September	119 786	IBD	Birth	0.95[*]	0.91-1.00	Unadjusted estimates reported
				Season of birth: October-December	119 786	IBD	Birth	1.01[*]	0.96-1.05	Unadjusted estimates reported
	Haslam, N. et al. 2000	UK	Diagnosed with CD between 1972 and 1989	Month of birth: January-June	Controls NR, 928 IBD	CD	Birth	1.14[§]	1.01-1.30	Unadjusted estimates reported
				Year of birth: Odd year	Controls NR, 928 IBD	CD	Birth	0.98[§]	0.84-1.14	Unadjusted estimates reported
	Holmes, E.A. et al. 2019	Australia	2010-2013	Sun exposure in Summer	495	IBD	0-2 years	1[*]	0.68-1.49	Unadjusted estimates reported
					495	IBD	3-5 years	0.8[*]	0.53-1.22	Unadjusted estimates reported
				Sun exposure in Winter	495	IBD	0-2 years	1[*]	0.66-1.51	Unadjusted estimates reported
					495	IBD	3-5 years	0.7[*]	0.44-1.10	Unadjusted estimates reported
	Thorsen, S.U. et al. 2016	Denmark	Born bewteen 1981–2004	Perinatal Vitamin D	768	IBD	Perinatal	1.12[**]	0.88-1.42	Variables adjusted for: 25(OH)D, gender, ethni- city, birth weight (categorical), gestational age (categorical) and mother's age (categorical)
	Van Ranst, M. et al. 2005	Belgium	Born between January 1, 1935 and December 31, 1990	Seasonality/Month of birth	6 150	CD	Birth	0.64[*]	0.45-0.91	Unadjusted estimates reported
	Lopez-Serrano, P. et al. 2010	Spain	2004	Season of birth- Winter	359	CD	Birth	1.2[*]	0.2-3.2	Unadjusted estimates reported
					424	UC	Birth	1.2[*]	0.3-2.8	Unadjusted estimates reported
				Season of birth- Spring	359	CD	Birth	0.8[*]	0.3-3.4	Unadjusted estimates reported
					424	UC	Birth	0.8[*]	0.3-2.4	Unadjusted estimates reported
				Season of birth- Summer	359	CD	Birth	0.9[*]	0.5-2.8	Unadjusted estimates reported
					424	UC	Birth	1[*]	0.5-3.4	Unadjusted estimates reported
				Season of birth- Autumn	359	CD	Birth	0.9[*]	0.5-2.8	Unadjusted estimates reported
					424	UC	Birth	1[*]	0.5-3.4	Unadjusted estimates reported
	Disanto, G. et al. 201	Scotland, England	1997 to 2009	Month of birth January	32 275 977	CD	Birth	1.06[*]	1.01-1.11	Unadjusted estimates reported
				Month of birth February	32 275 977	UC	Birth	1.04[*]	0.99-1.09	Unadjusted estimates reported
				Month of birth April	32 275 977	CD	Birth	0.96[*]	0.91-1.01	Unadjusted estimates reported
					32 275 977	UC	Birth	1.06[*]	1.02-1.11	Unadjusted estimates reported
				Month of birth August	32 275 977	CD	Birth	1.04[*]	0.99-1.10	Unadjusted estimates reported
					32 275 977	UC	Birth	0.97[*]	0.93-1.02	Unadjusted estimates reported
				Month of birth October	32 275 977	CD	Birth	0.92[*]	0.87-0.97	Unadjusted estimates reported
					32 275 977	UC	Birth	0.93[*]	0.88-0.97	Unadjusted estimates reported
	Lee, J. et al. 2020	South Korea	January 1997 and August 2015	Birth Month	17 246 154	CD	Birth	1.042[*]	1.009-1.076	Unadjusted estimates reported
					17 246 154	UC	Birth	1.032[*]	1.011-1.053	Unadjusted estimates reported
	Canova, C. et al. 2020	Italy	Born between 1982 and 2012	Birth season (October-April vs May-September)	1 804	IBD	Birth	1.19[**]	0.86-1.65	Adjusted for sex, year of birth, season of birth, having older sibilins, number of births, birth weight, gestational age; Apgar score at 1 minute, maternal age and mother's education

Study type	Study	Study location	Study Time Period	Exposure Description	Total sample size (n)	Outcome	Period of exposure	Effect estimate type (odds ratio, relative risk, rate ratio etc)	Effect estimate value	Confidence Interval (specify of different from 95% CI)	p-value	Comments
Cohort Studies												
	Khalili, H. et al. 2013	Boston, USA	1976-2008	Breastfeeding (yes/no)	1676264 person-years	CD	Infancy	MV-adjusted HR	0.99**	0.76-1.30	NS	Adjusted for smoking, BMI, birthweight, preterm birth, history of diabetes in the mother, maternal history of smoking during preganancy and oral contraceptive use.
					1676264 person-years	UC	Infancy	MV-adjusted HR	1.03**	0.81-1.31	NS	Adjusted for smoking, BMI, birthweight, preterm birth, history of diabetes in the mother, maternal history of smoking during preganancy and oral contraceptive use.
				Breastfed ≤3 months (compared with no breastfeeding)	1676264 person-years	CD	Infancy	MV-adjusted HR	1.26**	0.83-1.93	NS	Adjusted for smoking, BMI, birthweight, preterm birth, history of diabetes in the mother, maternal history of smoking during preganancy and oral contraceptive use.
					1676264 person-years	UC	Infancy	MV-adjusted HR	1.09**	0.73-1.72	NS	Adjusted for smoking, BMI, birthweight, preterm birth, history of diabetes in the mother, maternal history of smoking during preganancy and oral contraceptive use.
				Breastfed 4-8 mos (compared with no breastfeeding)	1676264 person-years	CD	Infancy	MV-adjusted HR	0.94**	0.66-1.32	NS	Adjusted for smoking, BMI, birthweight, preterm birth, history of diabetes in the mother, maternal history of smoking during preganancy and oral contraceptive use.
					1676264 person-years	UC	Infancy	MV-adjusted HR	0.97**	0.65-1.46	NS	Adjusted for smoking, BMI, birthweight, preterm birth, history of diabetes in the mother, maternal history of smoking during preganancy and oral contraceptive use.
				Breastfed ≥9 months (compared with no breastfeeding)	1676264 person-years	CD	Infancy	MV-adjusted HR	1.02**	0.63-1.66	NS	Adjusted for smoking, BMI, birthweight, preterm birth, history of diabetes in the mother, maternal history of smoking during preganancy and oral contraceptive use.
					1676264 person-years	UC	Infancy	MV-adjusted HR	0.90**	0.56-1.46	NS	Adjusted for smoking, BMI, birthweight, preterm birth, history of diabetes in the mother, maternal history of smoking during preganancy and oral contraceptive use.
	Burnett, D. et al. 2017	Nova Soctia, Canada	1988-2014	Breastfeeding	262 729	IBD	Infancy	aHR	1.09**	0.84-1.41	NS	Adjusted for maternal age, parity, area-level income, rural residence, smoking, weight status, and birth weight for gestational age
Case-Control Studies												
	Gearry, R.B. et al. 2010	Canterbury, New Zealand	June 2003 to May 2005	Breastfeeding	1238	CD	Infancy	aOR	0.55**	0.41-0.74	Not reported	Adjusted for family history of IBD, smoking, age at recruitment, social class at birth, ethnic identity and sex; BF significant when >3 months
					1253	UC	Infancy	aOR	0.71**	0.52-0.96	Not reported	Adjusted for family history of IBD, smoking, age at recruitment, social class at birth, ethnic identity and sex; BF significant when >3 months
	Ekbom, A. et al. 1990	Uppsala county, Sweden	1924-1957	Exclusive breastfeeding	607	CD	Infancy	crude OR	1*	0,5-2,2	Not reported	Unadjusted estimates reported
					678	UC	Infancy	crude OR	0.8*	0,5-1,4	Not reported	Unadjusted estimates reported
					771	IBD	Infancy	crude OR	0.9*	0,5-1,4	Not reported	Unadjusted estimates reported
	Baron, S. et al. 2005	Northern France	1988-1997	Breastfeeding	444	CD	Infancy	aOR	2.1**	1.3-3.4	0,003	Adjusted for mother's educational level
	Amre, D.K. et al. 2006	Montreal, Canada	1995-2004	Breastfeeding birth-6 mos	388	CD	Infancy	aOR	1.1**	0.7-1.9	Not reported	Adjusted for age, gender, family history of IBD, maternal smoking and social class
				Breastfeeding 7-12 mos	388	CD	Infancy	aOR	1.3**	0.7-2.6	Not reported	Adjusted for age, gender, family history of IBD, maternal smoking and social class
				Breastfeeding >1 year	388	CD	Infancy	aOR	1.6**	0.5-5.1	Not reported	Adjusted for age, gender, family history of IBD, maternal smoking and social class
	Basson, A. et al. 2014	Western Cape, South Africa	September 2011-January 2013	Breastfed as an infant	407	CD	Infancy	aOR	0.74**	0.39-1.41	<0,05	Adjusted for age at study enrolment, gender and ethnicity
	Radon, K. et al. 2007	Germany	March 2006 to August 2006	Nutrition other than breastmilk at 5 months	1931	CD	Infancy	aOR	0.9**	0.7-1.3	Not reported	Adjusted for age, gender, region, and parental education and mutually adjusted for IBD parental history, birth weight, maternal smoking during pregnancy, siblings, rhinitis and residence in urban area
					1791	UC	Infancy	aOR	0.7**	0.5-0.9	Not reported	Adjusted for age, gender, region, and parental education and mutually adjusted for IBD parental history, birth weight, maternal smoking during pregnancy, siblings, rhinitis and residence in urban area
	Salgado, V.C. et al. 2017	Brazil	Not Reported	Breastfeeding	308	CD	Infancy	aHR	0.77**	0.28-2.09	0,616	Adjusted for sex, age, race, educational level, family income, residence, housing conditions, family size in adulthood and childhood, pets, exposure to untreated water, vaccination (childhood), viral diseases (childhood), helmintic infections, exposure to enteric pathogens, previous appendicetomy, tobacco exposure and family history
	Russel, M.G. et al. 1998	Netherlands	October 1991 to July 1997	Breastfeeding	Not reported	CD	Infancy	Not reported	Not reported		NS	The authors only report that breastfeeding was not associated with the development of IBD, except in patients with pancolitis (see below)
					Not reported	UC	Infancy	OR	2*	1.0-3.9	NS	Only OR reported is in patients with ulcerative pancolitis
	Persson, P.G. et al. 1993	Stockholm	1984-1987	Breastfeeding	457	CD	Infancy	RR	Not reported		Not reported	RR of CD associated with breastfeeding was close to unity (data not shown)
					250	UC	Infancy	RR	Not reported		Not reported	Same for RC (close to unity; data not shown)
	Corrao, G. et al. 1998	Italy	1989-1992	Breastfeeding	450	CD	Infancy	OR	1.9*	1.1-3.3	< 0.05	Unadjusted estimates reported. 81.3% CD vs 86.7% in controls
					1188	UC	Infancy	OR	1.5*	1.1-2.1	< 0.05	Unadjusted estimates reported. 81.3% UC vs 86.4% in controls
	Jiang, L. et al. 2007	China	2004	Breastfeeding	354	UC	Infancy	OR	0.8*	0.47-1.37	0,42	Unadjusted estimates reported.
	Jakobsen, C. et al. 2013	Danmark	2007-2009	Breastfeeding > 3 months compared with ≤3 months	592	IBD	Infancy	aOR	0.5**	0.3-1.0	0,058	Adjusted for age, gender, ethnicity, area of residence and socioeconomic status
					533	UC	Infancy	aOR	0.5**	0.2-1.0	0,06	Adjusted for age, gender, ethnicity, area of residence and socioeconomic status
	Hlavaty, T. et al. 2013	Slovakia	2008-2009	Breastfeeding 0-5 months	545	CD	Infancy	aOR	2.716**	1.674-4.409	< 0.001	Adjusted for smoking at diagnosis, contact with cats in childhood, and sports activity in childhood
					503	UC	Infancy	aOR	1.692**	1.022-2.801	0,041	Adjusted for sports activity and family size in childhood
				Breastfeeding 6-12 months	545	CD	Infancy	Not reported	Not reported		Not reported	34% CD vs 56% controls
					503	UC	Infancy	Not reported	Not reported		Not reported	43% vs 56% controls
	Han, D.Y. et al. 2010	New Zeland	Not Reported	Breastfeeding	851	CD	infancy	OR	0.97*	0.58-1.61	0,9	Unadjusted estimates reported.
	Hansen, T.S. et al. 2011	Denmark	2003-2004	Breastfeeding	534	IBD	Infancy	OR	1.07*	0.52-2.16	NS	Unadjusted estimates reported.
					534	CD	Infancy	OR	1.8*	0.6-5.38	NS	Unadjusted estimates reported.
					534	UC	Infancy	OR	0.7*	0.2-1.84	NS	Unadjusted estimates reported.
				Breastfeeding more than 6 months	534	IBD	Infancy	OR	0.5*	0.23-1.11	NS	Unadjusted estimates reported.
					534	CD	Infancy	OR	0.63*	0.2-1.91	NS	Unadjusted estimates reported.
					534	UC	Infancy	OR	0.4*	0.13-1.28	NS	Unadjusted estimates reported.
	Thompson, N.P. et al. 1995	UK	1950-1968	Breastfeeding	2792	CD	Infancy	OR	1.04*	0.88-1.25	Not reported	Unadjusted estimates reported.
					1426	UC	Infancy	OR	1.16*	0.90-1.50	Not reported	Unadjusted estimates reported.
	Thompson, N.P. et al. 2000	UK	1946-1958	Breastfed	287	CD	Infancy	OR	0.4*	0.5-1.03	0,06	Unadjusted estimates reported.
					287	UC	Infancy	OR	2.76*	0.86-9.81	0,1	Unadjusted estimates reported.
	Ng, S.C. et al. 2015	Asia and Australia	April 2011 to March 2013	Breastfeeding for 7-12 mos, compared with 0-6 mos	1176	CD	Infancy	aOR	0.086**	0.03-0.243	significant at p<0.0006 level after Bonferroni adjustment.	Adjusted for sex, age and country income based on GNI. †5
					1196	UC	Infancy	aOR	0.142**	0.073-0.277	significant at p<0.0006 level after Bonferroni adjustment.	Adjusted for sex, age and country income based on GNI. †5
				Breastfeeding for >12 mos, compared with 0-6 mos	1176	CD	Infancy	aOR	0.542**	0.310-0.949	0,032	Adjusted for sex, age and country income based on GNI. †5
					1196	UC	Infancy	aOR	1.05**	0.708-1.557	0,809	Adjusted for sex, age and country income based on GNI. †5
	Samuelsson, S.M. et al. 1991	Uppsala county, Sweden	1945-1964	Weaning before 14 days	334	UC	Infancy	OR	1.2*	0.31-2.78	NS	Unadjusted estimates reported.
					334	Extensive UC	Infancy	OR	1*	0.35-2.86	NS	Unadjusted estimates reported.
					334	Non-progressive UC	Infancy	OR	1.67*	0.40-6.98	NS	Unadjusted estimates reported.
	Gilat, T. et al. 1987	International IBD Study group	Not Reported	Breastfeeding frequency	1497	IBD	Infancy	not reported	Not reported		NS	N/A
				Breastfeeding duration	1497	IBD	Infancy	not reported	Not reported		NS	N/A
				Frequency of formula feeding	1497	IBD	Infancy	not reported	Not reported		NS	N/A
				Type of formula feeding	1497	IBD	Infancy	not reported	Not reported		NS	N/A
				Added sugar to formula/milk	1497	IBD	Infancy	not reported	Not reported		NS	N/A
				Age of starting mixed feeedings	1497	IBD	Infancy	not reported	Not reported		NS	N/A
	Whorwell, P.J. et al. 1979	Southampton, UK	Not Reported	Breastfeeding	204	UC	Infancy	OR	lower odds	Not reported	0,005	N/A
					228	CD	Infancy	not reported	Not reported		NS	NA
				Bottlefeeding	204	UC	Infancy	OR	higher odds	Not reported	0,005	N/A
					228	CD	Infancy	not reported	Not reported		0,005	N/A
	Wang, Y.-F. et al. 2013	China	April 2007 to April 2010	Breastfeeding	2616	UC	Infancy	OR	1.08*	0.79-1.477	0,628	Unadjusted estimates reported.
	Van Limbergen, J.E. et al. 2009	Scotland	Not Reported	Breastfeeding	252	IBD	Infancy	not reported	Not reported		0,71	52% cases vs 55% controls
	Levy, L.C. et al. 2012	USA	Not Reported	Breastfeeding	832	CD	Infancy	aOR	0.272**	0.087-0.855	Not reported	Adjusting variables not reported
					626	UC	Infancy	not reported	Not reported		NS	N/A
	Niewiadomski, O. et al. 2016	Barwon, Australia	2007,2008 2010-2013	Breastfeeding	184	CD	Infancy	OR	Not reported		0,548	Unadjusted estimates reported.
					154	UC	Infancy	OR	Not reported		0,18	Unadjusted estimates reported.
	Doyle, J.B. et al. 2017	Northern Ireland	1971-1986	Breast vs bottle-feeding (day 10)	67173	IBD	Infancy	crude OR	1.05*	0.75-1.47	0,79	Unadjusted estimates reported.
	Decker, E. et al. 2010	Germany	May 2008 to May 2009	Breastfeeding	1117	CD	Infancy	aOR	0.99**	0.95-1.01	0,335	Adjusted for potential confounders such as mode of delivery or postnatal complications; Shorter duration of breastfeeding (3.53 vs 5.25 mos, p 0.004)
				Breastfeeding	912	UC	Infancy	aOR	0.93**	0.89-0.98	0,006	Adjusted for potential confounders such as mode of delivery or postnatal complications; Shorter duration of breastfeeding (4.24 vs 5.25 mos, p 0.026)
	Bernstein, C.N. et al. 2006	Manitoba, Canada	Not Reported	Breastfeeding	797	CD	Infancy	Not reported	Not reported		>0.26	43,8% CD vs 45% controls
					650	UC	Infancy	Not reported	Not reported		>0.26	50% UC vs 45% controls
	Bergstrand, O. et al. 1983	Stockholm county	1955-1974	Breastfeeding	616	CD	Infancy	Mean difference in breastfeeding duration	1.17 mos¶	Not reported	<0.01	CD associated with no or very short duration of breastfeeding
	Ananthakrishnan, A.N. et al. 2015	Boston, USA	Not Reported	Breastfeeding	895	IBD	Infancy	aOR	0.23**	0.14-0.36	Not reported	Demonstrated differences in the distribution of risk alleles suggest potential interactions between immunologic pathways contributing to IBD pathogenesis and early exposures influencing the host microbiome
	Vahedi, H. et al. 2011	Iran	2008-2009	Breastfeeding	380	CD	Infancy	not reported	Not reported		0,47	Adjusting variables not reported
					652	UC	Infancy	not reported	Not reported		0,33	N/A
				Formula feeding	380	CD	Infancy	not reported	Not reported		0,19	N/A
					652	UC	Infancy	not reported	Not reported		0,92	N/A
				Cow milk	380	CD	Infancy	not reported	Not reported		0,13	N/A
					652	UC	Infancy	not reported	Not reported		0,58	N/A
	Hutfless, S., et al. 2012	Northern California	1996-2006	Formula versus exclusive breast feeding	3269	IBD	infancy	aOR	1.1**	0.2-6.1	Not reported	Adjusted for at least sex and race
	Klein, I. et al. 1998	Israel	1992-1993	Breastfeeding	109	CD	Infancy	Not reported	Not reported		Not reported	74% vs 80%; only extracted population controls
					131	UC	Infancy	Not reported	Not reported		Not reported	76% vs 80%
	Urashima, H. et al. 1999	Japan	1979-1993	Breastfeeding	168	CD	Infancy	OR	0.3*	0.13-0.70	Not reported	Unadjusted estimates reported. Breastfeeding only or mixed compared to artificial feeding
					399	UC	Infancy	OR	0.53*	0.31-0.89	Not reported	Unadjusted estimates reported.
	Striscuglio, C. et al. 2017	Italy	2000-2014	Breastfeeding >3 months	305	CD	Infancy	aOR	4.3**	1.6-10.5	0,002	Adjusted for mother's educational level, father's employment, gluten introduction, number of siblings, autoimmune diseases, pets and bed sharing
				Gluten <6th month	305	CD	Infancy	aOR	2.8**	1.5-5	0,001	Adjusted for mother's educational level, father's employment, breast feeding, number of siblings, autoimmune diseases, pets and bed sharing
					365	UC	Infancy	aOR	2.8**	1.6-4.9	<0.001	Adjusted for mother's educational level, father's employment, breast feeding, number of siblings, autoimmune diseases, pets and bed sharing
	Sonntag, B. et al. 2007	Germany	January 2003 to March 2004	Breastfeeding	1974	CD	Infancy	OR	0.831*	0.68-1.015	Not reported	Unadjusted estimates reported. 67.6% CD vs 71.5% controls
					1641	UC	Infancy	OR	1.015*	0.812-1.267	Not reported	Unadjusted estimates reported. 71.8% UC vs 71.5% controls
	Senagapalli, S. et al. 2015	Australia	Not Reported	Breastfeeding	Not reported	IBD	Infancy	OR	0.389*	0.21-0.71	0,002	Unadjusted estimates reported.
	Gruber, M. et al. 1996	Western New York, USA	Not Reported	Breastfeeding	144	IBD	Infancy	OR	0.604*	0.29-1.3	0,183	Unadjusted estimates reported.
	Lopez-Serrano, P. et al. 2010	Spain	2004	Breastfeeding	359	CD	Infancy	OR	0.3*	0.05-0.1	0,001	Unadjusted estimates reported.
					385	UC	Infancy	OR	1.4*	0.6-3	0,385	Unadjusted estimates reported.
	van der Sloot, K. et al. 2020	Netherlands	Not Reported	Breastfeeding < 3 months	1671	CD	Infancy	MVaOR	0.56**	0.37-0.87	0.01	Adjusted for gender, age, smoking status at diagnosis
					1669	UC	Infancy	MVaOR	0.84**	0.54-1.31	0.45	Adjusted for gender, age, smoking status at diagnosis
				Breastfeeding > 3 months	1671	CD	Infancy	MVaOR	0.84*	0.57-1.23	0.36	Adjusted for gender, age, smoking status at diagnosis
					1669	UC	Infancy	MVaOR	0.98*	0.65-1.48	0.93	Adjusted for gender, age, smoking status at diagnosis

	Authors and Year	Study location	Study Time Period	Exposure Description	Total sample size (n)	CD/UC/IBD	Period of exposure	Effect estimate value	Confidence interval (specify of different from 95% CI)	Comments
Cohort Studies										
	Aspberg, S. et al. 2006	Sweden	1987-2000	parity 1 compared with ≥2	1479216	CD	0-5 yrs	1.15*	0.95-1.40	Unadjusted estimates reported
					1479216	UC	0-5 yrs	1.17*	0.99-1.39	Unadjusted estimates reported
	Bager, P. et al. 2012	Denmark	1973–2008	Hallmintic Infection (Filled prescription for Mebendazole)	924749	IBD	0-2 yrs old	0.9*	0.42-1.93	Adjusted for age, sex, calendar period, birth order, average gross annual income based on total household income, degree of urbanization, birth place of parents, and any parental diagnoses of the specific outcome.
					924749	IBD	3-5 years old	1.13*	0.7-1.62	Adjusted for age, sex, calendar period, birth order, average gross annual income based on total household income, degree of urbanization, birth place of parents, and any parental diagnoses of the specific outcome.
	Benchimol, E.I. et al. 2017	Canada	Alberta: 1999–2008, Manitoba and Ontario: 1999–2010, and Nova Scotia: 2000–2008	rural vs urban living	2633	IBD	0-5 years old	0.75-0.78*	≥1 years (0. 58–0.96), ≥2 years (0.59–0.96), ≥3 years (0.54–1.01), ≥4 years (0.50–1.00), and ≥5 years (CI 0.51–1.00)	Adjusted for age, sex and neighborhood income
	Burnett, D. et al. 2020	Canada	1988-2014	Living area (Urban vs. Rural) Administrative cohort	42906	IBD	0-5 yrs		Not signifcant	N/A
				Living area (Urban vs. Rural) Clinical cohort	262705	IBD	0-5 yrs		Not signifcant	N/A
	Elten, M. et al. 2020	Canada	April 1st, 1991 and March 31st, 2014	Living area (Urban vs. Rural)	2218789	IBD	0-5 yrs		Not signifcant	N/A
	Klement E. et al. 2008	Israel	1998-2004	birth order (2 vs 1)	123919	IBD	Birth	1.1**	0.91-1.32	Adjusted for gender, place of origin, number of siblings and place of living
				birth order (3 vs 1)	93164	IBD	Birth	1.26**	1.02-1.55	Adjusted for gender, place of origin, number of siblings and place of living
				birth order (4 vs 1)	35592	IBD	Birth	1.51**	1.09-2.09	Adjusted for gender, place of origin, number of siblings and place of living
				birth order (≥5 vs 1)	20025	IBD	Birth	2.35**	1.47-3.77	Adjusted for gender, place of origin, number of siblings and place of living
	Lange, A. et al. 2014	Denmark	1995-2009	Urban life	979039	CD	0-5 yrs	1.4*	1.0-1.8	Unadjusted estimates reported
				First born	979039	CD	Infancy	1.2†	0.8-1.7	Unadjusted estimates reported
	Ponsonby, A.L. et al. 2009	Victoria, Australia	1983–1998	Living in urban area compared with not urban	702900	CD	Perinatal	1.46**	1.07-1.99	Adjusted for sex, abormality, interventional birth, urban, married, SES, maternal age and year of birth
				Birth order (Later born vs firstborn)	998828	CD	Perinatal	0.96**	0.74-1.25	Adjusted for sex, abormality, interventional birth, urban, married, SES, maternal age and year of birth
	Timm, S. 2014	Northern Europe	1945-1973	Livestock farm compared with city	10864	IBD	0-5 yrs	0.55*	0.31-0.98	Adjusted for age, sex, smoking and BMI
				Village compared with city	10864	IBD	0-5 yrs	0.75*	0.52-1.10	Adjusted for age, sex, smoking and BMI
Case-Control Studies										
	Amre, D.K. et al. 2006	Montreal, Canada	1995-2004	Owning a pet during pregnancy	388	CD	Pregnancy	0.9**	0.5-1.6	Adjusted for age, gender, family history of IBD, maternal smoking and maternal education
				Owning a pet between birth - 5 years of age	388	CD	0-5 yrs	1.2**	0.7- 2.2	Adjusted for age, gender, family history of IBD, maternal smoking and maternal education
				Number of older siblings (0,1,≥2)	388	CD	0-5 yrs	Not Reported	Not reported	N/A
	Basson, A. et al. 2014	Western Cape, South Africa	September 2011 and January 2013	Piped or bottled water, compared with water from outside sources	407	CD	0-5 yrs	2.1**	1.2-4.0	Adjusted for age at study enrolment, ethnicity and gender
				Access to hot piped water	407	CD	0-5 yrs	1.18**	0.71-2.0	Adjusted for age at study enrolment, ethnicity and gender
				Suburban or urban community compared with rural/farm/informal settlement	407	CD	0-5 yrs	1.21**	0.71-2.1	Adjusted for age at study enrolment, ethnicity and gender
				≤5 persons in household, compared with ≥6	407	CD	0-5 yrs	0.68**	0.43-1.09	Adjusted for age at study enrolment, ethnicity and gender
				≤3 persons sharing bathroom compared with ≥4 persons	407	CD	0-5 yrs	0.55**	0.31-0.97	Adjusted for age at study enrolment, ethnicity and gender
				≥3 bedrooms compared with ≤2	407	CD	0-5 yrs	0.87**	0.69-1.11	Adjusted for age at study enrolment, ethnicity and gender
				Flush toilet compated with bucket/pit latrine/no facility	407	CD	0-5 yrs	1.35**	0.69-2.63	Adjusted for age at study enrolment, ethnicity and gender
				no pets compared with pets	407	CD	0-5 yrs	1.47**	0.92-2.34	Adjusted for age at study enrolment, ethnicity and gender
				No donkey/horse/cow/sheep on property compared with any present	407	CD	0-5 yrs	1.67**	0.83-3.45	Adjusted for age at study enrolment, ethnicity and gender
				no helminth infection compared with helminth infection	407	CD	0-5 yrs	0.87**	0.53-1.42	Adjusted for age at study enrolment, ethnicity and gender
				No treatment for heminth infection compared with treatment	407	CD	0-5 yrs	0.99**	0.60-1.63	Adjusted for age at study enrolment, ethnicity and gender
	Bernstein, C.N. et al. 2006	Manitoba, Canada	Not Reported	Living with pet cats before age 5	797	CD	0-5 yrs	0.66**	0.46-0.96	Adjusted for age and gender
					650	UC	0-5 yrs	0.68**	0.48-0.97	Adjusted for age and gender
				Number of household residents before age 5	797	CD	0-5 yrs	0.9*	0.83-0.97	Adjusted for age and gender
	Bernstein, C.N. et al. 2019	Canada	1970-2010	Rural vs urban	12159	IBD	Perinatal	0.91*	0.73- 1.15	Unadjusted estimates reported
	Boneberger, A. et al. 2011	Central South of Chile	June 2009 and February 2010	Rural place of living	226	UC	Infancy		Not reported	
				At least one older sibling	226	UC	0-5 yrs	2.2**	1.1-4.4	Adjusted for age (≤18 years/N18 years), sex (male/female), and rural place of living in the first year of life and mutually adjusted for at least one parent with Mapuche descent, High paternal education and pets
	Doyle, J.B. et al. 2017	Northern Ireland	1971–1986	Household Size	67173	IBD	Neonatal		Not Significant	
	Feeney, M.A. et al. 2002	UK	Not Reported	No older siblings	278	CD	0-5 yrs	1.38*	0.37-5.20	Unadjusted estimates reported
					274	UC	0-5 yrs	0.94*	0.29-3.05	Unadjusted estimates reported
				One older sibling	278	CD	0-5 yrs	0.96*	0.25-3.65	Unadjusted estimates reported
					274	UC	0-5 yrs	1.25*	0.43-3.59	Unadjusted estimates reported
				Two older siblings	278	CD	0-5 yrs	1.71*	0.48-6.16	Unadjusted estimates reported
					274	UC	0-5 yrs	0.77*	0.27-2.25	Unadjusted estimates reported
				Person-to-room ratio in home	278	CD	0-5 yrs	1.1*	0.24-5.02	Unadjusted estimates reported
					274	UC	0-5 yrs	1.23*	0.46-3.27	Unadjusted estimates reported
				Urban environment	278	CD	0-5 yrs	0.59*	0.28-1.24	Unadjusted estimates reported
					274	UC	0-5 yrs	0.96*	0.41-2.23	Unadjusted estimates reported
				Cat in the home	278	CD	0-5 yrs	0.81*	0.41-1.63	Unadjusted estimates reported
					274	UC	0-5 yrs	1.27*	0.71-2.26	Unadjusted estimates reported
				Dog in the home	278	CD	0-5 yrs	0.65*	0.34-1.24	Unadjusted estimates reported
					274	UC	0-5 yrs	0.69*	0.35-1.34	Unadjusted estimates reported
				Bird in the home	278	CD	0-5 yrs	1.76*	0.75-4.14	Unadjusted estimates reported
					274	UC	0-5 yrs	0.99*	0.46-2.09	Unadjusted estimates reported
				Rodent in the home	278	CD	0-5 yrs	0.89*	0.43-1.81	Unadjusted estimates reported
					274	UC	0-5 yrs	0.6*	0.25-1.44	Unadjusted estimates reported
	Gearry, R.B. et al. 2010	Canterbury, New Zealand	June 1, 2003 and May 30, 2005	Town dwelling compared with city dwelling	1238	CD	Infancy	0.83**	0.61-1.13	Adjusted for family history of IBD, smoking status, age at recruitment, social class at birth, ethnic identity and sex
					1253	UC	Infancy	1.11**	0.82-1.51	Adjusted for family history of IBD, smoking status, age at recruitment, social class at birth, ethnic identity and sex
				Country dwelling compared with city dwelling	1238	CD	Infancy	0.83**	0.6-1.13	Adjusted for family history of IBD, smoking status, age at recruitment, social class at birth, ethnic identity and sex
					1253	UC	Infancy	1.24**	0.92-1.69	Adjusted for family history of IBD, smoking status, age at recruitment, social class at birth, ethnic identity and sex
				Vegetable garden	1238	CD	Infancy	0.49**	0.34-0.69	Adjusted for family history of IBD, smoking status, age at recruitment, social class at birth, ethnic identity and sex
					1253	UC	Infancy	0.66**	0.46-0.93	Adjusted for family history of IBD, smoking status, age at recruitment, social class at birth, ethnic identity and sex
	Gent, A.E. et al. 1994	UK	1988	Water tap	728	CD	0-5 yrs	1.8*	0.6-5.4	Unadjusted estimates reported
					728	UC	0-5 yrs	0.9*	0.5-1.7	Unadjusted estimates reported
				Hot Water tap	728	CD	0-5 yrs	5*	1.4-17.3	Unadjusted estimates reported
					728	UC	0-5 yrs	1.3*	0.7-2.2	Unadjusted estimates reported
				Separate Bathroom	728	CD	0-5 yrs	3.3*	1.3-8.3	Unadjusted estimates reported
					728	UC	0-5 yrs	1.3*	0.7-2.4	Unadjusted estimates reported
				Flush toilet	728	CD	0-5 yrs	1.1*	0.5-2.6	Unadjusted estimates reported
					728	UC	0-5 yrs	1.4*	0.7-2.5	Unadjusted estimates reported
				Mains drainage	728	CD	0-5 yrs	2.6*	0.9-7.3	Unadjusted estimates reported
					728	UC	0-5 yrs	1.2*	0.7-2.1	Unadjusted estimates reported
	Hampe, J. et al. 2003	Germany	July 1996 to January 1998	Tap Water	4615	IBD	0-5 yrs	0.94*	0.53-1.66	Unadjusted estimates reported
				Warm Tap Water	4615	IBD	0-5 yrs	1.25*	0.78-2.00	Unadjusted estimates reported
				Water Toilet	4615	IBD	0-5 yrs	1.4*	0.83-2.39	Unadjusted estimates reported
				birth rank ≥3 compared with <3	4615	IBD	Birth	0.68*	0.51-0.91	Unadjusted estimates reported
	Han, D.Y. et al. 2010	New Zealand	Not Reported	Pet Ownership	851	CD	<6 yrs	1.26*	0.92-1.73	Unadjusted estimates reported
				Regularly feed pets	851	CD	<6 yrs	0.82*	0.55-1.22	Unadjusted estimates reported
				Had a sandpit in the garden	851	CD	0-3 yrs	1.08*	0.8-1.45	Unadjusted estimates reported
	Hansen, T.S. et al. 2011	Denmark	2003-2004	Running Water	534	IBD	Infancy	0.5*	0.15-1.66	Adjusted for smoking status, appendectomy, tonsillectomy, usage of oral contraceptives, and consumption of fibre, sugar, coffee, and eggs and mutually adjusted with variables in analysis
					534	CD	Infancy	0.5*	0.05-5.51	Adjusted for smoking status, appendectomy, tonsillectomy, usage of oral contraceptives, and consumption of fibre, sugar, coffee, and eggs and mutually adjusted with variables in analysis
					534	UC	Infancy	0.5*	0.13-2.0	Adjusted for smoking status, appendectomy, tonsillectomy, usage of oral contraceptives, and consumption of fibre, sugar, coffee, and eggs and mutually adjusted with variables in analysis
	Ko, Y.-et al. 2015	Australia	Not Reported	Rural dweller in Middle Eastern Migrants	795	CD	Infancy	0.19**	0.41–0.41	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	UC	Infancy	0.09**	0.04–0.24	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	CD	0-5 yrs	035**	0.18–0.68	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	UC	0-5 yrs	0.12**	0.05–0.30	Adjusted for age, sex, cigarrete smoking and family history of IBD
				Pet ownership in Middle Eastern Migrants	795	CD	Infancy	0.28**	0.13–0.64	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	UC	Infancy	0.43*	0.03–0.93	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	CD	0-5 yrs	0.24**	0.11–0.52	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	UC	0-5 yrs	0.27**	0.13-0.57	Adjusted for age, sex, cigarrete smoking and family history of IBD
				Farm animal ownership in Middle Eastern Migrants	795	CD	Infancy	0.12**	0.03–0.43	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	UC	Infancy	0.13**	0.04–0.44	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	CD	0-5 yrs	0.1**	0.05–0.50	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	UC	0-5 yrs	0.13**	0.04-0.40	Adjusted for age, sex, cigarrete smoking and family history of IBD
				Sharing bedroom in Middle Eastern Migrants	795	CD	Infancy	0.47**	0.21–1.04	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	UC	Infancy	0.6**	0.28–1.3	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	CD	0-5 yrs	0.3**	0.16–0.80	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	UC	0-5 yrs	0.4**	0.19-0.97	Adjusted for age, sex, cigarrete smoking and family history of IBD
				Pet feeding in Middle Eastern Migrants	795	CD	Infancy	0.12**	0.04–0.37	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	UC	Infancy	0.1**	0.05–0.46	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	CD	0-5 yrs	0.1**	0.03–0.30	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	UC	0-5 yrs	0.13**	0.05-0.35	Adjusted for age, sex, cigarrete smoking and family history of IBD
				Access to Hot Water in Middle Eastern Migrants	795	CD	Infancy	1.71**	0.68–4.30	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	UC	Infancy	1.85**	0.78–4.36	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	CD	0-5 yrs	1.56**	0.63–3.87	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	UC	0-5 yrs	1.69**	0.71-3.99	Adjusted for age, sex, cigarrete smoking and family history of IBD
	Levy, L.C. et al. 2012	South India	Not Reported	Refrigerator	634	IBD	<5 yrs		Not reported	N/A
				receiving deworming treatment	634	IBD	<5 yrs		Not reported	N/A
	Malekzadeh, F. et al. 2009	Tehran, Iran	1998 to 2004	Home refrigerator and freezer	406	CD	0-5 yrs	2.08**	1.01-4.25	Adjusted for sex,tobacco use and current age
	Radon, K. et al. 2007	Germany	March 2006 and August 2006	Pets	1931	CD	Infancy	1**	0.8-1.3	Adjusted for study region, age in quartiles, gander, duration of exclusive breastfeeding, parental history of IBD, number of older siblings, highest parental education and maternal smoking during pregnancy
					1791	UC	Infancy	0.9**	0.6-1.2	Adjusted for study region, age in quartiles, gander, duration of exclusive breastfeeding, parental history of IBD, number of older siblings, highest parental education and maternal smoking during pregnancy
				Farm animals	1931	CD	Infancy	0.5**	0.3-0.9	Adjusted for study region, age in quartiles, gander, duration of exclusive breastfeeding, parental history of IBD, number of older siblings, highest parental education and maternal smoking during pregnancy
					1791	UC	Infancy	0.4**	0.2-0.8	Adjusted for study region, age in quartiles, gander, duration of exclusive breastfeeding, parental history of IBD, number of older siblings, highest parental education and maternal smoking during pregnancy
	Ramakrishna, B.S. et al. 2012	South India	Not Reported	Open Well	304	CD	0-5 yrs	0.36**	0.19-0.69	Adjusting variables not reported
					330	UC	0-5 yrs		Not reported	Adjusting variables not reported
				Applying Cow dung to Floor	304	CD	0-5 yrs	0.55**	0.30-0.99	Adjusting variables not reported
					330	UC	0-5 yrs		Not reported	Adjusting variables not reported
				Personal Towel	304	CD	0-5 yrs	3.13**	1.48-6.60	Adjusting variables not reported
					330	UC	0-5 yrs		Not reported	Adjusting variables not reported
		US cohort		Well Water	832	CD	0-5 yrs	0.271**	0.087-0.084	Adjusting variables not reported
					626	UC	0-5 yrs		Not reported	Adjusting variables not reported
				Mouth Wash	626	UC	0-5 yrs		Not reported	Adjusting variables not reported
	Sahu, M.K. et al. 2010	South India	Not Reported	Urban (compared with Rural) residence	415	CD	Neonatal		Not reported	N/A
					415	UC	Neonatal		Not reported	N/A
					415	CD	0-3 years		Not reported	N/A
					415	UC	0-3 years		Not reported	N/A
	Samuelsson, S.M. et al. 1991	Uppsala county, Sweden	1945-1964	Birth order (did not specifiy further)	334	UC	Perinatal	1.01*	0.92-1.12	Unadjusted estimates reported
					334	Extensive UC	Perinatal	1*	0.88-1.11	Unadjusted estimates reported
					334	Non-progressive UC	Perinatal	1.06*	0.89-1.25	Unadjusted estimates reported
	Strisciuglio, C. et al. 201	Italy	2000-2014	Increased number of toilets	663	CD	Neonatal	1.73*	Not reported	Unadjusted estimates reported
					663	UC	Neonatal	2.17*	Not reported	Unadjusted estimates reported
	Thompson, N.P. et al. 1995	England and Wales	1950-1968	Urban/rural maternal residence	2966	CD	Neonatal	1.01*	0.65-1.55	Unadjusted estimates reported
					1578	UC	Neonatal	1.17*	0.91-1.50	Unadjusted estimates reported
	Thompson, N.P. et al. 2000	UK	1946-1958	First born	287	CD	Birth	0.92*	0.34-2.47	Unadjusted estimates reported
					287	UC	Birth	1.34*	0.57-3.17	Unadjusted estimates reported
	van der Sloot, K. et al. 2020	Netherlands	Not Reported	Living area (rural vs large village)	1671	CD	0-5 yrs	0.61*	0.44-0.84	Unadjusted estimates reported
					1669	UC	0-5 yrs	1.08*	0.80-1.45	Adjusted for age, gender and smoking status at diagnosis
				Living area (rural vs urban)	1671	CD	0-5 yrs	1.67*	1.19-2.36	Adjusted for age, gender and smoking status at diagnosis
					1669	UC	0-5 yrs	1.2*	0.98-2.05	Adjusted for age, gender and smoking status at diagnosis
				Household Pets (< 1yr)	1671	CD	Infancy	0.3*	0.22-0.40	Adjusted for age, gender and smoking status at diagnosis
					1669	UC	Infancy	0.32*	0.24-0.44	Adjusted for age, gender and smoking status at diagnosis
				Household Pets (1-5 yrs)	1671	CD	1-5 yrs	0.37*	0.29-0.49	Adjusted for age, gender and smoking status at diagnosis
					1669	UC	1-5 yrs	0.33*	0.25-0.43	Adjusted for age, gender and smoking status at diagnosis

Reference #	Authors	Study location	Study Time Period	Exposure Description	Total sample size (n)	CD/UC/IBD	Period of exposure	Effect estimate value	Confidence interval (specify of different from 95% CI)	Comments
Cohort Studies										
	Aspberg, S. et al. 2006	Sweden	1987-2000	Maternal education (Comprehensive school compared with continuation school)	1479216	CD	0-5 yrs	1.09*	0.66-1.81	Unadjusted estimates reported
					1479216	UC	0-5 yrs	0.97*	0.69-1.37	Unadjusted estimates reported
				Maternal education (University or equivalent compared with continuation school)	1479216	CD	0-5 yrs	1.24*	0.84-1.84	Unadjusted estimates reported
					1479216	UC	0-5 yrs	0.99*	0.74-1.34	Unadjusted estimates reported
	Ponsonby, A.L. et al. 2009	Australia	1983–1998	Marrital status (not married vs married mother)	998877	CD	Perinatal	1.73*†	1.10-2.71	Adjusted for sex, abormality, interventional birth, urban, married, SES, maternal age and year of birth
				SES index mid compared with low	252084	CD	Perinatal	1.12*†	0.78-1.61	Adjusted for sex, abormality, interventional birth, urban, married, SES, maternal age and year of birth
				SES index high compared with low	248158	CD	Perinatal	1.06*†	0.73-1.53	Adjusted for sex, abormality, interventional birth, urban, married, SES, maternal age and year of birth
				SES index very high compared with low	248492	CD	Perinatal	1.47*†	1.04-2.07	Adjusted for sex, abormality, interventional birth, urban, married, SES, maternal age and year of birth
Case-Control Studies										
	Amre, D.K. et al. 2006	Montreal, Canada	1995-2004	Daycare birth-6 mos	388	CD	Infancy	4.5**	1.4-13.7	Adjusted for age, gender, family history of IBD, maternal smoking and social class (via maternal education)
				Daycare 7-12 mos	388	CD	Infancy	1.5**	0.8-2.9	Adjusted for age, gender, family history of IBD, maternal smoking and social class (via maternal education)
				Daycare1-3 years	388	CD	0-5 yrs	1.1**	0.5-1.6	Adjusted for age, gender, family history of IBD, maternal smoking and social class (via maternal education)
				Maternal education (none-grade 4, secondary, college/technical, university)	388	CD	0-5 yrs	Not Reported		N/A
				Paternal education (none-grade 4, secondary, college/technical, university)	388	CD	0-5 yrs	Not Reported		N/A
				Family income	388	CD	Birth	Not Reported		N/A
	Basson, A. et al. 2014	South Africa	September 2011 to January 2013	Daycare birth-6 mos	407	CD	Infancy	0.61**	0.35-1.06	Adjusted for age at study enrolment, gender and ethnicity
	Bernstein, C.N. et al. 2019	Canada	1970-2010	Socioeconomic status Q4	12159	IBD	Perinatal	1.37*	1.06-1.77	Unadjusted estimates reported
				Socioeconomic status Q5	12159	IBD	Perinatal	1.35*	1.01-1.79	Unadjusted estimates reported
	Boneberger, A. et al. 2011	Central South of Chile	June 2009 to February 2010	High paternal education	226	UC	0-5 yrs	2.1**	1.0-4.5	Adjusted for age (≤18 years/N18 years), sex (male/female), and rural place of living in the first year of life and mutually adjusted for Mapuche descent, high paternal education, pets, at least one older sibling
				Day care	226	UC	Infancy	Not Reported		Adjusted for age (≤18 years/N18 years), sex (male/female), and rural place of living in the first year of life and mutually adjusted for Mapuche descent, high paternal education, pets, at least one older sibling
	Canova, C. et al. 2020	Italy	1989-2012	Maternal education (Primary vs High school)	1 586	IBD	Perinatal	1.23**	0.87-1.76	Adjusted for sex, year of birth, season of birth, having older sibilins, number of births, birth weight, gestational age; Apgar score at 1 minute, maternal age and mother's education
				Maternal education (Primary vs University)	946	IBD	Perinatal	0.96**	0.53-1.76	Adjusted for sex, year of birth, season of birth, having older sibilins, number of births, birth weight, gestational age; Apgar score at 1 minute, maternal age and mother's education
	Doyle, J.B. et al. 2017	Northern Ireland	1971-1986	Socioeconomic Status	67173	IBD	Neonatal	Not Significant		N/A
	Eslahpazir, J. et al. 2017	Montreal, Canada	1980-2010	Maternal education	801	CD	0-5 yrs	Not Reported		Adjustment not reported/not applicable. Higher education was associated with lower odds of CD
				Paternal education	801	CD	0-5 yrs	Not Reported		Adjustment not reported/not applicable. Higher education was associated with lower odds of CD
	Feeney, M.A et al. 2002	UK	Not Reported	Social class 1 or 2	278	CD	0-5 yrs	0.78*	0.18-3.40	Unadjusted estimates reported
					274	UC	0-5 yrs	2.49*	0.65-9.54	Unadjusted estimates reported
				Social class 3 (M) or (N)	278	CD	0-5 yrs	0.49*	0.14-1.78	Unadjusted estimates reported
					274	UC	0-5 yrs	1.71*	0.46-6.36	Unadjusted estimates reported
				Social class 4 or 5	278	CD	0-5 yrs	0.5*	0.14-1.83	Unadjusted estimates reported
					274	UC	0-5 yrs	1.19*	0.31-4.56	Unadjusted estimates reported
				Attended nursery	278	CD	0-5 yrs	0.63*	0.28-1.39	Unadjusted estimates reported
					274	UC	0-5 yrs	0.5*	0.22-1.16	Unadjusted estimates reported
				Seldom use of swimming pool	278	CD	0-5 yrs	1.92*	0.87-4.22	Unadjusted estimates reported
					274	UC	0-5 yrs	1.48*	0.75-2.91	Unadjusted estimates reported
				Frequent use of swimming pool	278	CD	0-5 yrs	2.9*	1.21-6.91	Unadjusted estimates reported
					274	UC	0-5 yrs	1.19*	0.55-2.58	Unadjusted estimates reported
				No family car in 0-5 yrs	278	CD	0-5 yrs	1.62*	0.57-4.58	Unadjusted estimates reported
					274	UC	0-5 yrs	0.44*	0.15-1.31	Unadjusted estimates reported
				One family car in 0-5 yrs	278	CD	0-5 yrs	0.6*	0.26-1.38	Unadjusted estimates reported
					274	UC	0-5 yrs	0.53*	0.25-1.14	Unadjusted estimates reported
				No house moves	278	CD	0-5 yrs	1.39*	0.64-3.00	Unadjusted estimates reported
					274	UC	0-5 yrs	0.8*	0.34-1.87	Unadjusted estimates reported
				One house move	278	CD	0-5 yrs	1.78*	0.79-4.01	Unadjusted estimates reported
					274	UC	0-5 yrs	0.92*	0.45-1.87	Unadjusted estimates reported
	Gearry, R.B. et al. 2010	Canterbury, New Zealand	June 1, 2003 to May 30, 2005	Social class at birth- class 3-4 (ref class 1-2)	1238	CD	Birth	0.55**	0.41-0.75	Adjusted for family history of IBD, smoking status, age at recruitment, social class at birth, ethnic identity and sex
					1253	UC	Birth	0.65**	0.48-0.88	Adjusted for family history of IBD, smoking status, age at recruitment, social class at birth, ethnic identity and sex
				Social class at birth- class 5-6 (ref class 1-2)	1238	CD	Birth	0.74**	0.5-1.1	Adjusted for family history of IBD, smoking status, age at recruitment, social class at birth, ethnic identity and sex
					1253	UC	Birth	0.59**	0.4-0.88	Adjusted for family history of IBD, smoking status, age at recruitment, social class at birth, ethnic identity and sex
				Home-heating- wood (presence vs absence)	1238	CD	Infancy	0.82**	0.62-1.08	Adjusted for family history of IBD, smoking status, age at recruitment, social class at birth, ethnic identity and sex
					1253	UC	Infancy	0.83**	0.63-1.09	Adjusted for family history of IBD, smoking status, age at recruitment, social class at birth, ethnic identity and sex
				Home-heating- coal (presence vs absence)	1238	CD	Infancy	1.12**	0.86-1.45	Adjusted for family history of IBD, smoking status, age at recruitment, social class at birth, ethnic identity and sex
					1253	UC	Infancy	1.24**	0.96-1.61	Adjusted for family history of IBD, smoking status, age at recruitment, social class at birth, ethnic identity and sex
				Home-heating- electricity (presence vs absence)	1238	CD	Infancy	0.84**	0.65-1.08	Adjusted for family history of IBD, smoking status, age at recruitment, social class at birth, ethnic identity and sex
					1253	UC	Infancy	0.72**	0.56-0.93	Adjusted for family history of IBD, smoking status, age at recruitment, social class at birth, ethnic identity and sex
	Gilat, T. et al. 1987	International IBD Study group	Not Reported	primary school in mothers	1497	CD	0-5 yrs	Not reported		N/A
					1497	UC	0-5 yrs	lower odds	not reported	N/A
				primary school parents	1497	UC	0-5 yrs	- 0.71*	0.31-1.62	Unadjusted estimates reported. Negative estimate as reported in the study.
				university/ college education of parents	1497	CD	0-5 yrs	- 0.67*	0.45-1.00	Unadjusted estimates reported. Negative estimate as reported in the study.
	Hampe, J. et al. 2003	Germany	July 1996 to January 1998	Central heating	4615	IBD	0-5 yrs	1.31*	0.8-2.12	Unadjusted estimates reported
	Han, D.Y. et al. 2010	New Zealand	Not Reported	Takeaway consumption	851	CD	0-5 yrs	1.66*	1.15-2.38	Unadjusted estimates reported
				>50% home carpeted	851	CD	0-5 yrs	1.51*	1-2.26	Unadjusted estimates reported
				Lived in a house with a swimming pool for greater than one year	851	CD	0-5 yrs	0.69*	0.35-1.35	Unadjusted estimates reported
				Preschool	851	CD	0-5 yrs	1.29*	0.96-1.73	Unadjusted estimates reported
	Holmes, E.A. et al. 2019	Australia	2010-2013	Father's education	495	IBD	Prenatal	Not reported		N/A
				Mother's education	495	IBD	Prenatal	Not reported		N/A. IBD with higher "Trade cert or other", lower "University qualification" or "Secondary school or less"
	Ko, Y. et al. 2015	Australia	Not Reported	Takeaway consumption in middle eastern migrants	795	CD	Infancy	1.97*	0.03-2.88	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	UC	Infancy	1.22*	0.56-2.34	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	CD	0-5 yrs	2.65*	0.08-0.86	Adjusted for age, sex, cigarrete smoking and family history of IBD
					795	UC	0-5 yrs	3.96*	0.19-8.18	Adjusted for age, sex, cigarrete smoking and family history of IBD
	Lopez-Serrano, P. et al. 2010	Spain	2004	Parental occupation (higher skill level)	783	CD	0-5 yrs	1.83*	1.14-2.95	Unadjusted estimates reported
					783	UC	0-5 yrs	2.04*	1.31-3.17	Unadjusted estimates reported
	Ramakrishna, B.S. et al. 2012	USA and India	Not Reported	0-5 yrs daycare	832	CD	0-5 yrs	0.083**	0.0181-0.811	Adjusting variables not reported
					626	UC	0-5 yrs	Not reported		N/A
	Samuelsson, S.M. et al. 1991	Uppsala County, Sweden	1945-1964	Paternal SES (middle vs high)	334	UC	Birth	0.87*	0.41-1.86	Unadjusted estimates reported
					334	Extensive UC	Birth	0.58*	0.21-1.57	Unadjusted estimates reported
					334	Non-progressive UC	Birth	2.8*	0.56-13.88	Unadjusted estimates reported
				Paternal SES (low vs high)	334	UC	Birth	0.66*	0.30-1.42	Unadjusted estimates reported
					334	Extensive UC	Birth	0.27*	0.09-0.75	Unadjusted estimates reported
					334	Non-progressive UC	Birth	6.13*	1.08-34.53	Unadjusted estimates reported
	Strisciuglio, C. et al. 2017	Campania, Southern Italy	2000-2014	Maternal degree	305	CD	0-5 yrs	5.5**	2.5-11.6	Adjusted for breast feeding, father's employment, gluten introduction, no. Of siblings, autoimmune diseases, pets and bed sharing

Study type	Study	Study Location	Study Time Period	Exposure Description	Total sample size (n)	Outcome	Period of Exposure	Effect estimate value	Confidence interval (specify if different from 95% CI)	Comment
Cohort Studies										
	Agrawal, M. et al. 2020	Denmark	1977-1995	Second-Generation Immigrants	8700000	IBD	Birth	1.07[‡§]	0.8-1.43	Adjusted for sex, age (0–9, 10–14, 15–74 in 1-year intervals and ≥75 years) and calendar time (1-year intervals).
			1996-2003		8700000	IBD	Birth	0.69[‡]	0.56-0.86	
			2004-2009		8700000	IBD	Birth	0.78‡‡	0.67-0.92	
			2010-2014		8700000	IBD	Birth	0.96[‡]	0.85-1.08	
			2015-2018		8700000	IBD	Birth	1.13[‡§]	1.01-1.26	
				Second-Generation Female Immigrants	8700000	IBD	Birth	0.89[‡§]	0.81-0.98	
				Second-Generation Female Immigrants from country of low IBD risk	8700000	IBD	Birth	0.84[‡§]	0.59-1.19	
				Second-Generation Female Immigrants from country of moderate IBD risk	8700000	IBD	Birth	0.96[‡§]	0.87-1.00	
				Second-Generation Female Immigrants from country of high IBD risk	8700000	IBD	Birth	0.69[‡§]	0.49-0.96	
				Second-Generation Male Immigrants	8700000	IBD	Birth	1.06[‡§]	0.97-1.17	
				Second-Generation Male Immigrants from country of low IBD risk	8700000	IBD	Birth	1.06[‡§]	0.76-1.48	
				Second-Generation Male Immigrants from country of moderate IBD risk	8700000	IBD	Birth	1.02[‡§]	1.08-1.33	
				Second-Generation Male Immigrants from country of high IBD risk	8700000	IBD	Birth	0.7[‡§]	0.49-0.99	
			1977-2018	First Generation Immigrants	8700000	IBD	0-5 yrs	1.07‡‡	0.9-1.27	Adjusted for sex, age (0–9, 10–14, 15–74 in 1-year intervals and ≥75 years), calendar time (1-year intervals) and continent of birth
			1977-2018		8700000	CD	0-5 yrs	0.95‡‡	0.72-1.26	
			1977-2018		8700000	UC	0-5 yrs	1.14‡‡	0.92-1.42	
	Ghersin, I. et al. 2019	Israel	2002-2016	Maternal country of birth- Israel	1144213	CD	Birth	reference		Adjusting variables include age, gender and diagnosis. Other variables that were included by forward selection: country of origin (Israel, western countries, former USSR, Asia, Africa, Ethiopia), num- ber of children in the household (0-2, ≥3), and socioeconomic status (high, medium, low)
					1144213	UC	Birth	reference		
				Maternal region of birth- West	1144213	CD	Birth	1.2[§§]	1.09-1.32	
					1144213	UC	Birth	0.69[§§]	0.58-0.82	
				Maternal country of birth- Former USSR	1144213	CD	Birth	0.71[§§]	0.6-0.82	
					1144213	UC	Birth	0.55[§§]	0.43-0.67	
				Maternal country of birth- Asia	1144213	CD	Birth	0.61[§§]	0.5-0.73	
					1144213	UC	Birth	0.71[§§]	0.60-0.82	
				Maternal country of birth- North Africa	1144213	CD	Birth	0.75[§§]	0.66-0.85	
					1144213	UC	Birth	0.47[§§]	0.37-0.57	
				Maternal country of birth- Ethiopia	1144213	CD	Birth	0.52[§§]	0.43-0.62	
					1144213	UC	Birth	0.49[§§]	0.33-0.67	
				Paternal country of birth- Israel	1144213	CD	Birth	reference		
					1144213	UC	Birth	reference		
				Paternal region of birth- West	1144213	CD	Birth	1.15[§§]	1.002-1.33	
					1144213	UC	Birth	0.77[§§]	0.62-0.95	
				Paternal country of birth- Former USSR	1144213	CD	Birth	0.65[§§]	0.54-0.77	
					1144213	UC	Birth	0.6[§§]	0.47-0.77	
				Paternal country of birth- Asia	1144213	CD	Birth	0.59[§§]	0.49-0.71	
					1144213	UC	Birth	0.66[§§]	0.52-0.84	
				Paternal country of birth- North Africa	1144213	CD	Birth	0.91[§§]	0.78-1.04	
					1144213	UC	Birth	0.67[§§]	0.52-0.85	
				Paternal country of birth- Ethiopia	1144213	CD	Birth	0.41[§§]	0.27-0.63	
					1144213	UC	Birth	0.22[§§]	0.10-0.48	
	Benchimol, E.I. et al. 2015	Canada	1994–2009	All second-generation immigrants compared with children of nonimmigrants	2144660	IBD	Birth	0.63[†]	0.53-0.75	Adjusted for age and sex
					2144660	CD	Birth	0.49[†]	0.38-0.63	
					2144660	UC	Birth	0.78[†]	0.60-1.01	
				Second-generation East Asia and Pacific compared with with children of nonimmigrants	2144660	IBD	Birth	0.11[†]	0.05-0.25	
					2144660	CD	Birth	0.13[†]	0.05-0.34	
					2144660	UC	Birth	0.1[†]	0.03-0.41	
				Second-generation Eastern Europe and Central Asia compared with children of nonimmigrants	2144660	IBD	Birth	0.6[†]	0.36-0.99	
					2144660	CD	Birth	0.34[†]	0.14-0.82	
					2144660	UC	Birth	0.66[†]	0.30-1.49	
				Second-generation Latin America and Caribbean compared with children of nonimmigrants	2144660	IBD	Birth	0.66[†]	0.45-0.98	
					2144660	CD	Birth	0.48[†]	0.27-0.88	
					2144660	UC	Birth	0.71[†]	0.38-1.33	
				Second-generation Middle East and North Africa compared with children of nonimmigrants	2144660	IBD	Birth	0.94[†]	0.57-1.53	
					2144660	CD	Birth	0.61[†]	0.27-1.35	
					2144660	UC	Birth	1.63[†]	0.87-3.05	
				Second-generation South Asia compared with with children of nonimmigrants	2144660	IBD	Birth	0.83[†]	0.63-1.09	
					2144660	CD	Birth	0.57[†]	0.37-0.89	
					2144660	UC	Birth	1.11[†]	0.74-1.68	
				Second-generation Sub-Sahara Africa compared with children of nonimmigrants	2144660	IBD	Birth	0.63[†]	0.37-1.09	
					2144660	CD	Birth	0.59[†]	0.28-1.24	
					2144660	UC	Birth	0.68[†]	0.28-1.64	
				Second-generation Western Europe and North America compared with children of nonimmigrants	2144660	IBD	Birth	1.15[†]	0.77-1.72	
					2144660	CD	Birth	1.15[†]	0.68-1.96	
					2144660	UC	Birth	1.2[†]	0.62-2.32	
	Montgomery, S.M. et al. 1999	United Kingdom	April 5-11, 1970	Second-generation Indian/Pakistani/Bangladeshi	8432	IBD	Birth	7.02[**]	2.39-20.65	Adjusted for sex and household crowding
				Second-generation West Indian/Guyanese	8432	IBD	Birth	3.47[**]	0.47-25.87	
	Li, X. et al. 2011	Sweden	1986–2007	All second-generation immigrants		CD	Birth	0.98[#]	0.94-1.02	Adjusted for age (in 5- year groups), gender, time period, socio-economic status, and geographical region-specific
						UC	Birth	0.98[#]	0.94-1.03	
				Second-generation from Denmark		CD	Birth	1.17[#]	1.02-1.35	
						UC	Birth	1.09[#]	0.95-1.24	
				Second-generation from Finland		CD	Birth	0.83[#]	0.77-0.90	
						UC	Birth	1.07[#]	1.00-1.14	
				Second-generation from Norway		CD	Birth	1.13[#]	0.99-1.29	
						UC	Birth	0.93[#]	0.81-1.06	
				Second-generation from Greece		CD	Birth	0.99[#]	0.67-1.42	
						UC	Birth	0.56[#]	0.34-0.88	
				Second-generation from Italy		CD	Birth	1.30[#]	0.87-1.85	
						UC	Birth	0.81[#]	0.51-1.23	
				Second-generation from Spain		CD	Birth	0.85[#]	0.45-1.46	
						UC	Birth	0.66[#]	0.33-1.18	
				Second-generation from Great Britain and Ireland		CD	Birth	1.00[#]	0.67-1.44	
						UC	Birth	0.66[#]	0.41-1.00	
				Second-generation from Germany		CD	Birth	1.12[#]	0.96-1.30	
						UC	Birth	0.99[#]	0.85-1.15	
				Second-generation from Austria		CD	Birth	1.20[#]	0.81-1.72	
						UC	Birth	1.14[#]	0.79-1.59	
				Second-generation from Yugoslavia		CD	Birth	1.19[#]	0.97-1.44	
						UC	Birth	0.60[#]	0.46-0.76	
				Second-generation from Romania		CD	Birth	1.39[#]	0.76-2.34	
						UC	Birth	0.65[#]	0.26-1.35	
				Second-generation from Estonia		CD	Birth	0.85[#]	0.62-1.13	
						UC	Birth	1.09[#]	0.85-1.38	
				Second-generation from Poland		CD	Birth	1.02[#]	0.77-1.32	
						UC	Birth	0.96[#]	0.74-1.24	
				Second-generation from Hungary		CD	Birth	1.26[#]	0.92-1.69	
						UC	Birth	0.87[#]	0.61-1.20	
				Second-generation from Chile		CD	Birth	0.49[#]	0.28-0.80	
						UC	Birth	0.91[#]	0.62-1.31	
				Second-generation from Turkey		CD	Birth	0.89[#]	0.68-1.15	
						UC	Birth	0.86[#]	0.65-1.12	
				Second-generation from Lebanon		CD	Birth	1.20[#]	0.80-1.73	
						UC	Birth	1.02[#]	0.60-1.64	
				Second-generation from Iran		CD	Birth	1.16[#]	0.87-150	
						UC	Birth	1.55[#]	1.14-2.06	
				Second-generation from Iraq		CD	Birth	1.85[#]	1.28-2.59	
						UC	Birth	1.19[#]	0.72-1.83	
Case-Control Studies										
	Bernstein, C.N. et al. 2006	Manitoba, Canada	Not Reported	First generation Canadian (born in Canada), compared with controls	797	CD	Birth	0.33[**]	0.17-0.62	Adjusted for age and gender
				First generation Canadian (born in Canada), compared with UC	797	CD	Birth	0.5[**]	0.31-0.83	
	van der Sloot, K. et al. 2020	Netherlands	Not Reported	Non-Western Migration (2nd generation)	1671	CD	0-5 yrs	1.2[**]	0.38-3.78	Adjusted for gender, age, and smoking status at diagnosis [never/former/current]
					1669	UC	0-5 yrs	1.42**	0.46-4.38	

Study tupe	Study	Study Location	Study Time Period	Exposure Description	Total sample size (n)	Outcome	Period of exposure	Effect estimate value	Confidence interval (specify if different from 95% CI)	Comments
Cohort Studies										
	Lange, A. et al. 2014	Denmark	1995-2009	Antibiotics or infections requiring hospitalization	979039	CD	Infancy	1.4††	1-1.8	Adjusted for family history of CD, mode of delivery, birth order, year of birth, gestational age, rural vs urban residence, maternal smoking, and NSAID use in infancy
Case-Control Studies										
	Amre, D.K. et al. 2006	Montreal, Canada	1995-2004	Physician-diagnosed childhood infections	388	CD	0-5 yrs	0.9**	0.6, 1.5	Adjusted for age, gender, family history of IBD, maternal smoking, and maternal education
	Axelrad J.E. et al. 2019	Sweden	2002-2014	Gastroenteritis	480721	IBD	0-5 yrs	1.09**	1.01–1.16	Adjusted for sex, age, birth year, place of residence, and previous gastrointestinal surgery, autoimmune disease, and family history of IBD
	Bernstein, C.N. et al. 2019	Manitoba, Canada	1970-2010	Infections	12159	IBD	Infancy	1.39*	1.09-1.79	Unadjusted estimates reported
	Ekbom, A. et al. 1990	Sweden	1924-1957	Postnatal infection	771	IBD	Perinatal	5.5¶	2.6-11.8	Unadjusted estimates reported
	Hildebrand, H. et al. 2008	Sweden	1973-1997	Otitis media	7648	CD	0-5 yrs	1.61**	0.89-2.92	Adjusted for maternal age
				Pneumonia	7648	CD	0-5 yrs	3.56**	1.79-7.08	
	Shaw, S.Y. et al. 2013	Canada	1989-2008	Otitis media	2671	IBD	0-5 yrs	2.8**	1.5-5.23	Adjusted for cumulative number of non–gastrointestinal-related physician v
					2671	CD	0-5 yrs	2.69**	1.23-5.9	
					2671	UC	0-5 yrs	3.02**	1.07-8.5	
	Springmann, V. et al. 2014	Quebec, Canada	1988-2005	Infection	2030	CD	0-5 yrs	0.98**	0.77-1.24	Adjusted for age, gender, and area of residence
				Infection	2030	CD	Infancy	0.98**	0.74-1.3	
	Strisciuglio, C. et al. 2017	Italy	2000-2014	Infections or hospitalizations	467	IBD	Infancy	Not Reported		
				Infections such as measles, mumps, smallpox, rubella	467	IBD	0-5 yrs	Not Reported		
	Thompson, N.P. et al. 1995	United Kingdom	1950-1968	Exposure to measles	2244	CD	Pregnancy (first trimester)	1,11	0.93-1.32*	Unadjusted estimates reported
					2244	CD	Pregnancy (second trimester)	0,93	0.79-1.11*	
					2244	CD	Pregnancy (third trimester)	0,95	0.8-1.13*	
					2244	CD	At birth	0,88	0.74-1.06*	
					2244	CD	0-6 months	0,9	0.76-1.07*	
					2244	CD	Infancy	0,96	0.78-1.18*	
	Whorwell, P. J. et al. 1979	Southampton, United Kingdom	Not Reported	Gastroenteritis	228	CD	Infancy	Not Reported		
					204	UC	Infancy	Not Reported		

Study deisgn	Study	Study location	Study Time Period	Exposure Description	Total sample size (n)	Outcome	Period of exposure	Effect estimate value	Confidence interval (specify if different from 95% CI)	Comments
Cohort Studies										
	Nylund, C. et al. 2019	United States of America	Not Reported	Antibiotics	968468	CD	0-6 mos	1.34††	1.11-1.62	Adjusting variables not reported
					968468	UC		1.10††	0.84-1.44	
				Proton pump inhibitors	968468	CD		1.45††	0.86-2.42	
					968468	UC		3.76††	2.28-6.17	
				H2 receptor antagonists	968468	CD		1.34††	1.01-1.80	
					968468	UC		1.23††	0.83-1.83	
	Lange, A. et al. 2014	Denmark	1991-2000; 2001-2010	Antibiotics or infections requiring hospitalization	979 039	CD	Infancy	1.4††	1-1.8	Adjusted for family history of CD, mode of delivery, birth order, year of birth, gestational age, rural vs urban residence, maternal smoking, and NSAID use in infancy
	Kronman, M.P. et al. 2012	United Kingdom	1994-2009	Antibiotics at ≤1 year of age	1072426	IBD	Infancy	5.51††	1.66-18.28	Adjusted for family history of IBD, gender, chronic granulomatous disease, primary sclerosing cholangitis, and socioeconomic deprivation
				1-2 courses of antiaerobic antibiotics	1072426	IBD	Infancy	3.33††	1.69-6.58	
				>2 antiaerobic antibiotics	1072426	IBD	Infancy	4.77††	2.13-10.68	
				Antibiotics at ≤5 years of age	1072426	IBD	0-5 yrs	2.62††	1.61-4.25	
	Ortqvist, A.K. et al. 2017	Sweden	2006-2013	Antibiotics	827239	IBD	Infancy	1.11††	0.57-2.15	Adjusted for mother's and father's history of IBD, parental education, mother's and father's country of birth and mode of delivery
					827239	CD	Infancy	0.72††	0.27-1.92	
					827239	UC	Infancy	1.23††	0.45-3.39	
Case-Control studies										
	Shaw S.Y. et al. 2010	Canada	1996-1997, 2007-2008	Antibiotics	396	IBD	Infancy	2.9*	1.21-6.96	Unadjusted estimates reported
	Hviid, A. et al. 2010	Denmark	1995-2003	Antibiotics use in the previous 3 months	577627	CD	0-2 mos	NA	1.08-3.15	Adjusted for age (in 1-year intervals) and calendar period (in 1-year intervals)
					577627	CD	3-11 mos	3.32**	1.15-9.56	
					577627	CD	Infancy	1.53**	0.15-15.46	
					577627	CD	2-3 yrs	3.73**	1.02-13.60	
				Antibiotic use >3 months previously	577627	CD	0-2 mos	4.19**	1.64-10.68	
					577627	CD	3-11 mos	1.04**	0.53-2.04	
					577627	CD	Infancy	1.11**	0.52-2.35	
					577627	CD	2-3 yrs	2.17**		
	Han, D.Y. et al. 2010	New Zealand	Not Reported	Any regular medication	851	CD	< 6 yrs	1.36*	0.65-2.83	Unadjusted estimates reported
				≥4 antibiotics/year	851	CD	< 6 yrs	2.19*	1.41-3.40	
	Troelsen, F. et al. 2020	United Kingdom	1998-2017	Antibiotics (ever vs never users)	5720	CD	0-5 yrs	2.2**	0.75-6.43	Adjusted for age (+/- 2 years), sex, general practice, and registration year in the registry
					5720	UC	0-5 yrs	1.07**	0.41-2.79	
				Antibiotics (1 prescription vs. none)	5720	CD	0-5 yrs	2.92**	0.85-10	
					5720	UC	0-5 yrs	1**	0.28-3.52	
				Antibiotics (2-4 prescriptions vs. none)	5720	CD	0-5 yrs	2.37**	0.77-7.11	
					5720	UC	0-5 yrs	1.01**	0.36-2.84	
				Antibiotics (5-9 prescriptions vs. none)	5720	CD	0-5 yrs	2.39**	0.79-2.27	
					5720	UC	0-5 yrs	1.05**	0.39-2.91	
				Antibiotics (10-19 prescriptions vs. none)	5720	CD	0-5 yrs	1.97**	0.63-6.12	
					5720	UC	0-5 yrs	1.06**	0.36-3.08	
				Antibiotics (≥20 prescriptions vs. none)	5720	CD	0-5 yrs	0.54**	0.90-3.25	
					5720	UC	0-5 yrs	1.75**	0.47-6.50	
	Canova, C. et al. 2020	Italy	1989-2012	Antibiotics	1804	IBD	0-6 mos	1.45**	0.80-2.62	Adjusted for sex; year of birth; season of birth; having older siblings; number of births; birth weight; gestational age; Apgar scores at 1 minute; maternal age; mother's formal education at the moment of birth and gastrointestinal infections (hospital discharge record diagnosis).
					1804	CD	0-6 mos	2.61**	1.17-5.81	
					1804	UC	0-6 mos	0.85**	0.29-2.52	
					1804	IBD	Infancy	1.07**	0.64-1.79	
					1804	CD	Infancy	1.72**	0.84-3.53	
					1804	UC	Infancy	0.72**	0.28-1.86	
	Gearry, R.B. et al. 2010	New Zealand	2003-2005	antibiotic use >4 times/year	1238	CD	Infancy	1.21**	0.78-1.58	Adjusting variables not reported
					1253	UC	Infancy	0.94**	0.58-1.51	

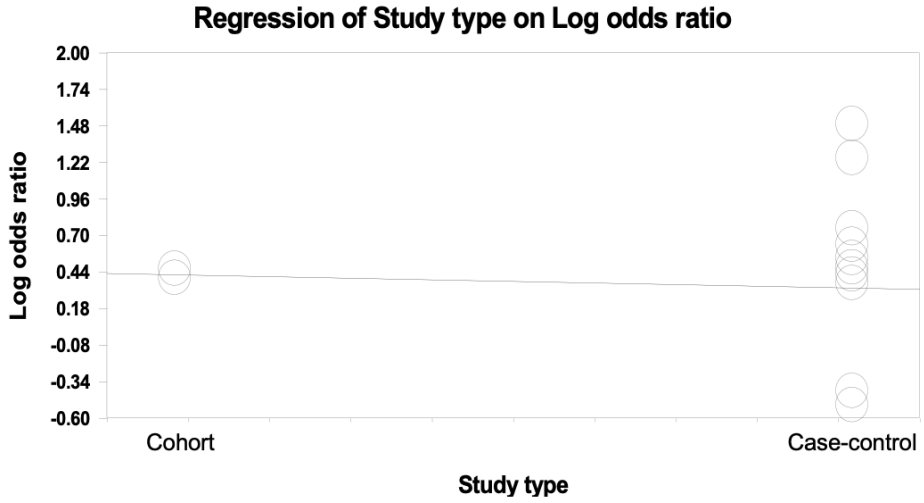
Study design	Study	Study Location	Study Time Period	Exposure Description	Total sample size (n)	Outcome	Period of exposure	Effect estimate value	Confidence interval (specify if different from 95% CI)	Comments
Case Control Studies										
	Thompson, N.P. et al. 1995	England	1950-1968	Passive smoking	3073	CD	0-5 yrs	1.04*	0.88-1.23	Unadjusted estimates reported. Note: total number of CD patients with controls.
					1654	UC	0-5 yrs	1.1*	0.90-1.50	Unadjusted estimates reported. Note: total number of UC patients with controls
	Han, D.Y. et al. 2010	New Zealand	Not Reported	Smoking Exposure	851	CD	0-5 yrs	1.19*	0.89-1.59	Unadjusted estimates reported. There was no significant association with smokers at home during the adolescence, childhood, or preschool period (p > 0.05).Represented OR children < 6 yrs
	Basson, A. et al. 2014	Western Cape, South Africa	September 20	Passive smoking	407	IBD	0-5 yrs	1.71**	1.01-2.94	Adjusted for age at study enrolment, gender and ethnicity

Case-control Studies										
Study (name, year)	**Selection**					**Comparability**	**Exposure**			
	1.Is the case definition adequate? (1 point)	2. Representativeness of the cases (1 point)	3. Selection of Controls (1 point)	4. Definition of Controls (1 point)	Total points for selection (4 points)	Comparability of cases and controls on the basis of the design or analysis (2 points)	1. Assessment of exposure (1 point)	2. Same method of ascertainment for cases and controls (1 point)	3. Non-Response rate (1 point)	Total points for outcome (3 points)
Amre, D.K. et al. 2006	1(a)	1(a)	0(b)	1(a)	3	2	1(b)	1(a)	1(a)	3
Ananthakrishnan, A.N. et al. 2015	0(c)	0(b)	0(c)	0(b)	0	1	0(c)	1(a)	0(c)	1
Axelrad, J. et al. 2019	1(a)	1(a)	1(a)	1(a)	4	2	1(a)	1(a)	0(c)	2
Bager, P. et al. 2012	0(b)	1(a)	1(a)	1(a)	3	2	0(d)	1(a)	1(a)	3
Baron, S. et al. 2005	1(a)	1(a)	1(a)	0(b)	3	2	1(b)	1(a)	1(a)	3
Basson, A. et al. 2014	1(a)	1(a)	1(a)	1(a)	4	2	0(c)	1(a)	1(a)	2
Bergstrand, O. et al. 1983	1(a)	0(b)	1(a)	0(b)	2	2	0(c)	1(a)	0(c)	1
Bernstein, C.N. et al. 2006	1(a)	1(a)	1(a)	0(b)	3	2	0(c)	1(a)	0(c)	1
Bernstein, C.N. et al. 2016	1(a)	1(a)	1(a)	1(a)	4	1	1(a)	1(a)	0(c)	2
Bernstein, C.N. et al. 2017	1(a)	1(a)	1(a)	1(a)	4	2	1(a)	1(a)	1(a)	3
Bernstein, C.N. et al. 2019	1(a)	1(a)	0(c)	1(a)	3	2	1(a)	1(a)	1(a)	3
Boneberger, A. et al. 2011	1(a)	1(a)	0(b)	1(a)	3	2	0(c)	1(a)	0(b)	1
Canova, C. et al. 2020	0(b)	1(a)	1(a)	1(a)	3	2	1(a)	1(a)	1(a)	3
Corrao, G. et al. 1998	1(a)	1(a)	1(a)	1(a)	4	1	1(b)	1(a)	1(a)	3
Davis, R.L. et al. 2001	0(b)	0(b)	0(c)	1(a)	1	1	1(a)	1(a)	1(a)	3
Decker, E. et al. 2010	0(b)	0(b)	0(b)	0(b)	0	2	0(c)	1(a)	0(c)	1
Disanto G. et al. 2012	0(c)	0(b)	1(a)	1(a)	2	1	1(a)	1(a)	0(c)	2
Doyle, J.B. et al. 2017	1(a)	0(b)	1(a)	1(a)	3	0	1(a)	1(a)	1(a)	3
Ekbom, A. et al. 1990	1(a)	1(a)	0(b)	0(b)	2	2	1(a)	1(a)	1(a)	3
Eslahpazir J. et al. 2017	1(a)	0(b)	1(a)	1(a)	4	1	1(b)	1(a)	0(c)	2
Feeney, M. et al. 1997	1(a)	1(a)	1(a)	0(b)	3	2	0(d)	1(a)	0(c)	1
Feeney, M. et al. 2002	1(a)	1(a)	0(b)	1(a)	3	0	0(c)	1(a)	0(c)	1
Gearry, R.B. et al. 2010	1(a)	1(a)	1(a)	1(a)	4	2	1(b)	1(a)	1(a)	3
Gent, A.E. et al. 1994	1(a)	0(b)	0(b)	1(a)	2	0	0(c)	1(a)	1(a)	2
Gilat, T. et al. 1987	0(b)	0(b)	0(b)	1(a)	1	2	0(c)	1(a)	0(b)	1
Gruber, M. et al. 1996	0(b)	1(a)	1(a)	0(b)	2	2	0(d)	1(a)	0(c)	1
Hampe, J. et al. 2003	1(a)	1(a)	1(a)	1(a)	4	0	1(b)	1(a)	0(c)	2
Han, D.Y. et al. 2010	1(a)	1(a)	1(a)	0(b)	3	0	0(d)	1(a)	1(a)	2
Hansen, T.S. et al. 2011	1(a)	1(a)	0(b)	1(a)	3	1	0(d)	1(a)	1(a)	2
Haslam, N. et al. 2000	1(a)	0(b)	0(c)	0(b)	1	1	1(a)	1(a)	0(c)	2
Hildebrand, H. et al. 2008	1(a)	1(a)	1(a)	1(a)	4	2	1(a)	1(a)	1(a)	3
Hlavaty, T. et al. 2013	1(a)	1(a)	1(a)	1(a)	4	2	0(d)	1(a)	0(c)	1
Holmes, E.A. et al. 2019	1(a)	1(a)	0(b)	1(a)	3	2	0(d)	1(a)	1(a)	2
Hutfless, S. et al. 2012	1(a)	0(b)	1(a)	0(b)	2	2	1(a)	1(a)	0(c)	2
Hviid, A. et al. 2011	1(a)	1(a)	1(a)	1(a)	4	2	1(a)	1(a)	1(a)	3
Jakobsen, C. et al. 2013	1(a)					2	0(d)			
Jiang, L. et al. 2007	1(a)	1(a)	1(a)	1(a)	4	1	0(c)	1(a)	1(a)	2
Klein, I. et al. 1993	1(a)	1(a)	1(a)	0(b)	3	0	0(c)	1(a)	1(a)	2
Ko, Y. et al. 2015	1(a)	0(b)	1(a)	1(a)	3	1	0(d)	1(a)	1(a)	2
Lavy, A. et al. 2001	1(a)	1(a)	1(a)	1(a)	4	1	0(c)	1(a)	1(a)	3
Lee, J. et al. 2020	0(b)	1(a)	0(c)	0(b)	1	0	1(a)	1(a)	0(c)	2
Levy, L.C. et al. 2012	0(c)	0(b)	0(c)	0(b)	0	2	0(c)	0(b)	0(c)	0
Lopez-Serrano, P. et al. 2010	1(a)	1(a)	0(b)	1(a)	3	2	0(d)	1(a)	0(c)	1
Mahid, S.S. et al. 2007	1(a)	0(b)	1(a)	0(b)	2	1	0(e)	1(a)	1(a)	2
Malekzadeh, F. et al. 2009	1(a)	1(a)	0(b)	1(a)	3	2	1(b)	1(a)	0(c)	2
Malmborg, P. et al. 2012	1(a)	1(a)	1(a)	1(a)	4	1	1(a)	1(a)	0(c)	2
Ng, S.C. et al. 2015	1(a)	1(a)	1(a)	1(a)	4	2	0(c)	1(a)	1(a)	2
Niewiadomski, O. et al. 2016	1(a)	0(b)	1(a)	1(a)	3	0	0(c)	1(a)	1(a)	2
Persson, R.G. et al. 1993	1(a)	1(a)	1(a)	1(a)	4	1	0(d)	1(a)	1(a)	2
Radon, K. et al. 2007	1(a)	1(a)	1(a)	1(a)	4	1	0(d)	1(a)	1(a)	2
Ramakrishna B.S. et al. 2012	0(c)	0(b)	0(c)	0(b)	0	2	1(b)	0(b)	0(c)	1
Russel, M.G. et al. 1998	1(a)	1(a)	1(a)	1(a)	4	1	0(d)	1(a)	1(a)	2
Russell, R K. et al. 2005	0(c)	0(b)	0(c)	0(b)	0	0	0 (e)	0(b)	0(c)	0
Sahu M.K. et al. 2010	0(c)	0(b)	1(a)	0(b)	1	0	1(b)	0(b)	0(c)	1
Salgado, V.C. et al. 2017	1(a)	1(a)	0(b)	1(a)	3	2	0(c)	1(a)	1(a)	2
Samuelson, S.M. et al. 1991	1(a)	1(a)	1(a)	0(b)	3	0	0(c)	1(a)	1(a)	2
Sanagapalli, S. et al. 2015	1(a)	1(a)	1(a)	1(a)	4	0	0(c)	1(a)	0(c)	1
Shaw, S.Y. et al. 2010	1(a)	0(b)	1(a)	1(a)	3	2	1(a)	1(a)	1(a)	3
Shaw, S.Y. et al. 2013	1(a)	1(a)	1(a)	1(a)	4	2	0(d)	1(a)	1(a)	3
Shaw, S.Y. et al. 2014	1(a)	1(a)	1(a)	1(a)	4	2	1(a)	1(a)	1(a)	3
Shaw, S.Y. et al. 2015	1(a)	1(a)	1(a)	1(a)	4	2	1(a)	1(a)	0(c)	2
Sonntag, B. et al. 2007	1(a)	0(b)	0(c)	1(a)	2	1	1(a)	1(a)	0(c)	2
Springmann, V. et al. 2014	1(a)	1(a)	1(a)	1(a)	4	1	0(d)	1(a)	1(a)	3
Strisciuglio, C. et al. 2017	1(a)	0(b)	1(a)	1(a)	3	2	0(c)	1(a)	0(c)	1
Thompson, N.P. et al. 1995	0(b)	0(b)	1(a)	0(b)	1	1	0(d)	1(a)	0(c)	1
Thompson, N.P. et al. 2000	1(a)	1(a)	1(a)	0(b)	3	0	0(c)	1(a)	1(a)	2
Thorsen, S.U. et al. 2016	1(a)	1(a)	1(a)	1(a)	4	2	1(a)	1(a)	1(a)	3
Troelsen, F.S. et al. 2019	0(b)	1(a)	1(a)	1(a)	3	0	1(a)	1(a)	0(c)	2
Urashima, H. et al. 1999	1(a)	1(a)	1(a)	1(a)	4	0	0(d)	1(a)	1(a)	2
Vahedi, H. et al. 2011	1(a)	0(b)	0(b)	0(b)	1	2	0(c)	1(a)	0(c)	1
van der Sloot, K.W.J. et al. 2020	0(c)	1(a)	1(a)	1(a)	3	1	0 (c/d)	1(a)	1(a)	2
Van Limbergen, J.E. et al. 2009	0(c)	0(b)	0(c)	0(b)	0	2	0(c)	0(b)	0(c)	0
Van Ranst, M. et al. 2005	1(a)					2	1(a)			
Vcev, A. et al. 2015	1(a)	1(a)	1(a)	1(a)	4	0	0(c)	1(a)	0(c)	1
Velosa, M. et al. 2019	0(b)	1(a)	1(a)	1(a)	3	2	1(a)	1(a)	0(c)	2
Villumsen M. et al. 2013	1(a)	1(a)	1(a)	1(a)	4	2	1(a)	1(a)	1(a)	3
Wang, Y.F. et al. 2013	0(b)	0(b)	1(a)	1(a)	2	2	0(c)	1(a)	0(c)	1
Whorwell, P. J. et al. 1979	0(c)	0(b)	1(a)	0(b)	1	0	0(c)	1(a)	0(c)	1
Yu, I. et al. 2016	1(a)	1(a)	0(c)	0(b)	2	0	0(d)	1(a)	0(c)	1

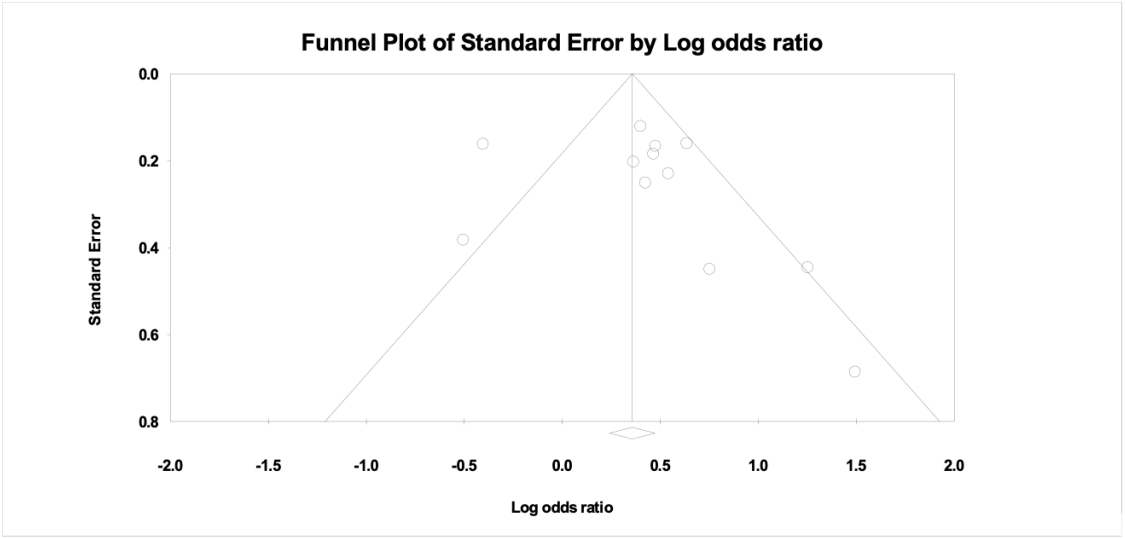
Cohort studies										
Study (name, year)	**Selection**					**Comparability**	**Outcome**			
	1.Representativeness of the exposed cohort (1 point)	2. Selection of the non exposed cohort (1 point)	3. Ascertainment of exposure (1 point)	4. Demonstration that outcome of interest was not present at start of study (1 point)	Total points for selection (4 points)	Comparability of cohorts on the basis of the design or analysis (2 points)	1. Assessment of outcome (1 point)	2. Was follow-up long enough for outcomes to occur (1 point)	3. Adequacy of follow up (1 point)	Total points for outcome (3 points)
Agrawal, M. et al. 2020	1(a)	1(a)	1(a)	1(a)	4	2	1(a)	1(a)	1(a)	3
Andersen, V. et al. 2013	1(a)	1(a)	1(a)	0(b)	3	2	1(b)	0(b)	0(d)	1
Andersen, V. et al. 2020	1(a)	1(a)	1(a)	1(a)	4	2	1(a)	1(a)	0(c)	2
Aspberg, S. et al. 2006	1(a)	1(a)	1(a)	1(a)	4	0	1(a)	1(a)	0(d)	2
Bager, P. et al. 2012	1(a)	1(a)	1(a)	0(b)	3	2	1(b)	1(a)	0(d)	2
Benchimol, E. et al. 2015	1(a)	1(a)	1(a)	1(a)	4	2	1(b)	1(a)	1(a)	3
Benchimol, E.I. et al. 2017	1(a)	1(a)	1(a)	1(a)	4	2	1(b)	0(b)	0(d)	1
Black, M. et al. 2015	1(a)	1(a)	0(a)	0(b)	2	2	1(b)	1(a)	0(c)	2
Black, M. et al. 2015	0(d)	1(a)	1(a)	1(a)	3	2	1(b)	1(a)	1(a)	3
Blomster, T.M. et al. 2014	1(a)	1(a)	1(b)	1(a)	4	2	1(b)	1(a)	1(b)	3
Burnett, D. et al. 2017	1(a)	1(a)	1(a)	1(a)	4	2	1(b)	1(a)	0(d)	2
Burnett, D. et al. 2020	1(a)	1(a)	1(a)	1(a)	4	2	1(b)	1(a)	0(c)	2
Card, T.R. et al. 2002	1(a)	1(a)	1(a)	1(a)	4	1	1(b)	1(a)	1(b)	3
Chowers, Y. et al. 2004	1(a)	1(a)	1(a)	1(a)	4	1	1(b)	1(a)	0(d)	2
Ekbom, A. et al. 1991	1(a)	1(a)	1(a)	1(a)	4	1	1(b)	1(a)	0(d)	2
Elten, M. et al. 2020	1(a)	1(a)	1(a)	0(b)	3	2	1(a)	1(a)	1(a)	3
Ghersin, I. et al. 2019	1(a)	1(a)	1(a)	1(a)	4	2	1(b)	0(b)	1(a)	2
Greenbaum, S. et al. 2018	1(a)	1(a)	0(d)	1(a)	3	2	0(d)	0(b)	0(d)	0
Khalili, H. et al. 2012	1(b)	1(a)	1(b)	1(a)	4	2	1(a)	1(b)	1(a)	3
Khalili, H. et al. 2013	1(a)	1(a)	1(a)	0(b)	3	2	1(b)	1(a)	1(b)	3
Klement, E. et al. 2008	1(a)	1(a)	1(b)	1(a)	4	2	1(b)	0(b)	1(b)	2
Konijeti, G. et al. 2013	1(a)	1(a)	1(b)	1(a)	4	2	1(b)	1(a)	1(b)	2
Kronman, M.P. et al. 2012	1(a)	1(a)	1(a)	1(a)	4	2	1(b)	1(a)	1(b)	3
Lange, A. et al. 2014	1(a)	1(a)	0(d)	0(b)	2	1	0(d)	1(a)	0(c)	1
Li, X. et al. 2011	1(a)	1(a)	1(a)	1(a)	4	2	1(b)	1(a)	1(b)	3
Montgomery, S.M. et al. 1999	1(a)	1(a)	1(a)	1(a)	4	2	1(a)1(b)	1(b)	1(a)	3
Morris, D.L. et al. 2000	1(a)	1(a)	1(b)	1(a)	4	1	1(b)	1(a)	1(b)	1
Nylund, C. et al. 2019	1(a)	1(a)	1(a)	0(b)	3	2	1(a)	1(a)	0(d)	2
Ortqvist, A.K. et al. 2019	1(a)	1(a)	1(a)	1(a)	4	2	1(b)	1(a)	1(b)	3
Ponsonby, A.L. et al. 2009	1(a)	1(a)	1(a)	0(b)	3	2	1(b)	1(a)	0(d)	2
Seagroatt, V. et al. 2003	1(a)	1(a)	1(a)	1(a)	4	0	1(a)	1(a)	0(d)	2
Sonnenberg, A. et al. 2009	1(a)	1(a)	1(a)	1(a)	4	1	1(b)	1(a)	1(b)	3
Steiner, N. et al. 2019	1(a)	1(a)	1(a)	1(a)	4	2	1(b)	1(a)	1(b)	3
Timm, S. et al. 2014	1(a)	1(a)	1(b)	1(a)	4	2	0(c)	1(a)	1(b)	2
Yoles, I. et al. 2018	1(b)	1(a)	1(a)	1(a)	4	1	1(b)	0(b)	0(d)	1

APPENDIX C: Supplementary Figures

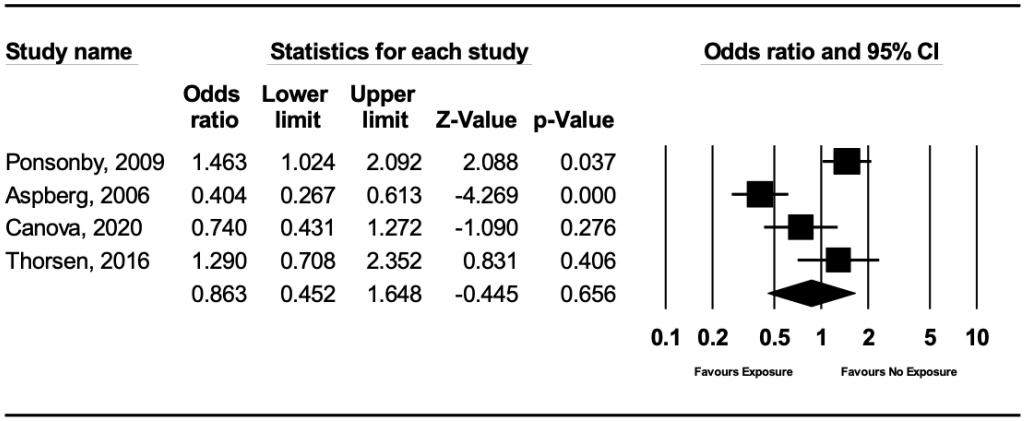
Supplementary Figure 1: Meta-regression of cohort vs case-control studies on the association between maternal smoking and subsequent IBD diagnosis in the offspring (P value of slope 0.45)



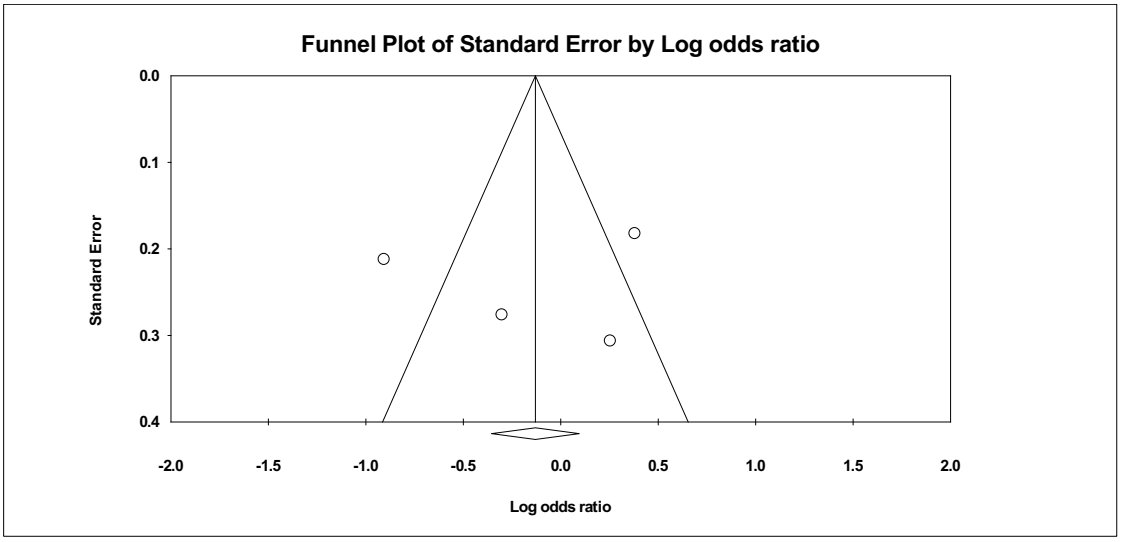
Supplementary Figure 2: Funnel plot to assess publication bias in studies on the association between maternal smoking and subsequent IBD diagnosis in the offspring (Egger's 2-sided p-value 0.451)



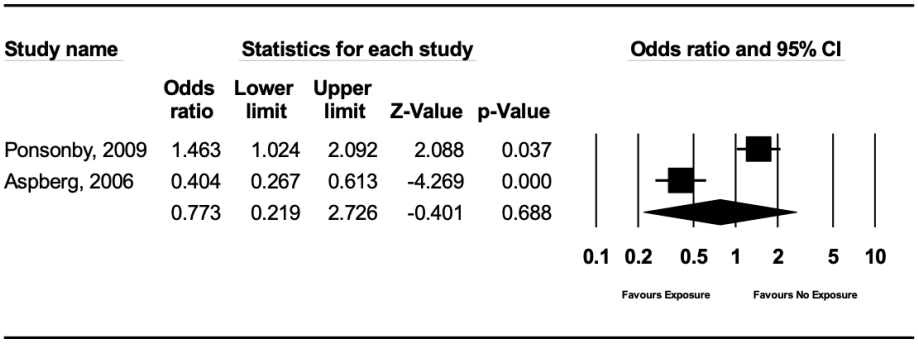
Supplementary Figure 3: Forest plot of the association between older maternal age and subsequent IBD diagnosis in the offspring (I^2 87.06%)



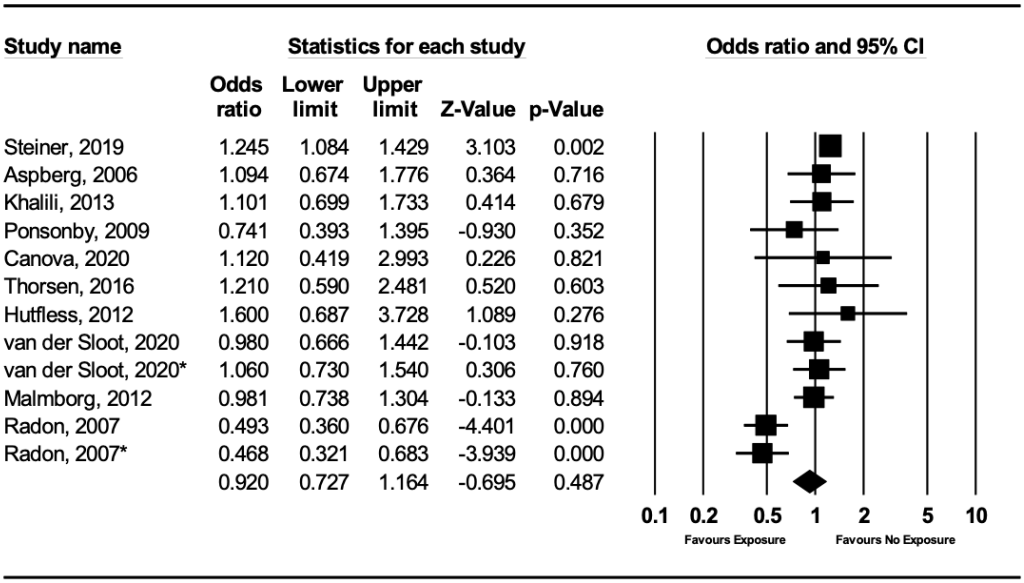
Supplementary Figure 4: Funnel plot to assess publication bias in studies on the association between older maternal age and subsequent IBD diagnosis in the offspring



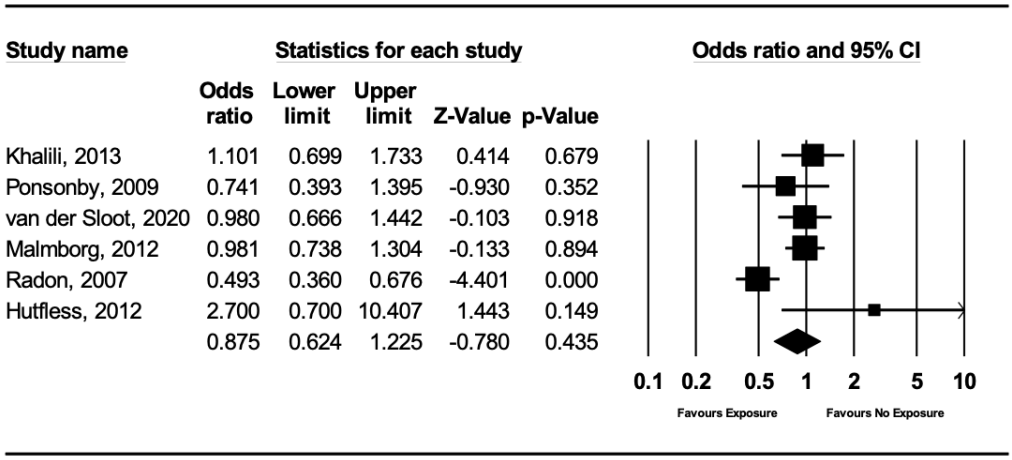
Supplementary Figure 5: Forest plot of the association between older maternal age and subsequent CD diagnosis in the offspring (I^2 95.27%)



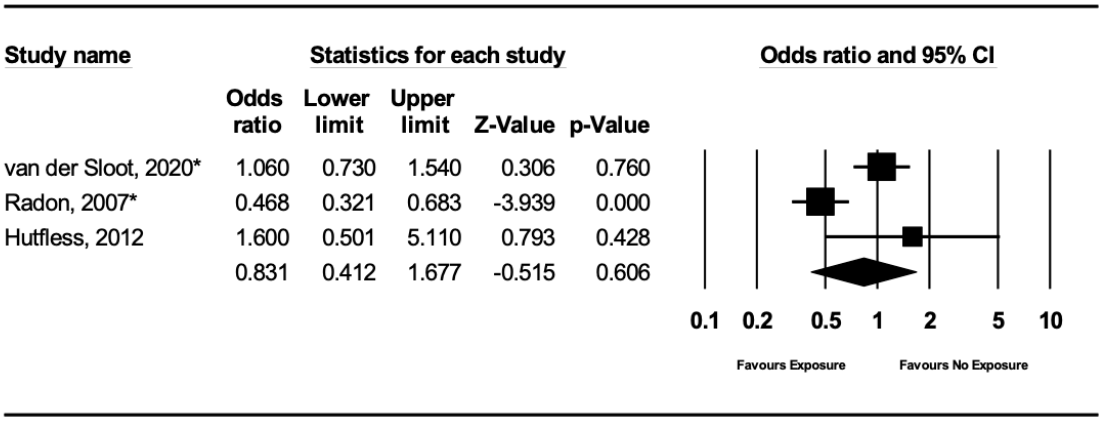
Supplementary Figure 6: Forest plot of the association between low birth weight and subsequent IBD diagnosis (I^2 76.75%)



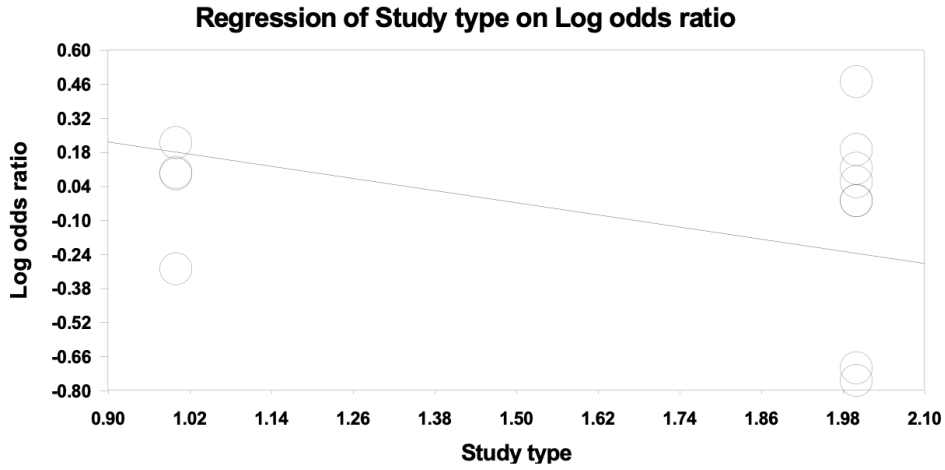
Supplementary Figure 7: Forest plot of the association between low birth weight and subsequent CD diagnosis (I^2 70.72%)



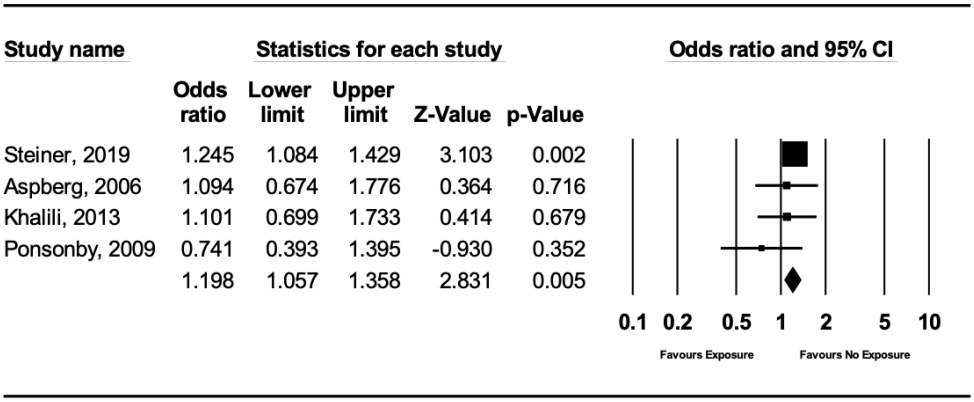
Supplementary Figure 8: Forest plot of the association between low birth weight and subsequent UC diagnosis (I^2 81.66%)



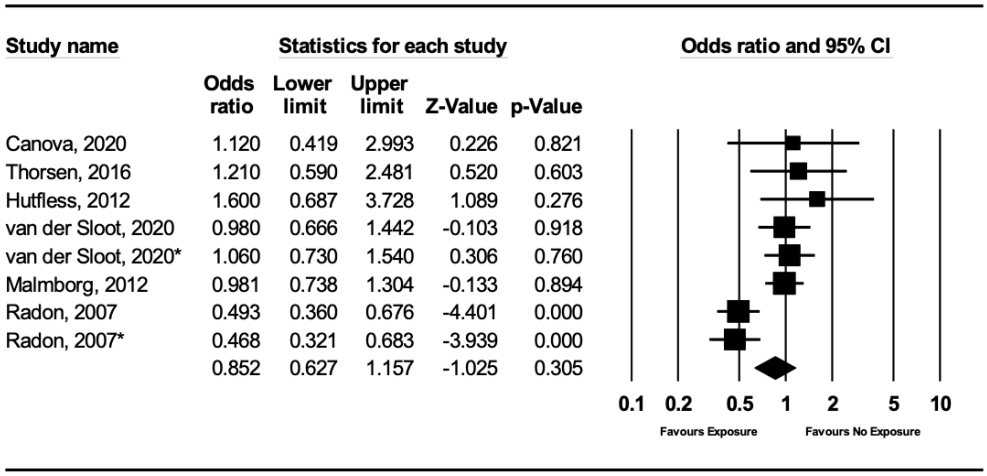
Supplementary Figure 9: Meta-regression of cohort vs case-control studies on the association between low birth weight and subsequent IBD diagnosis (P value of slope <0.001)



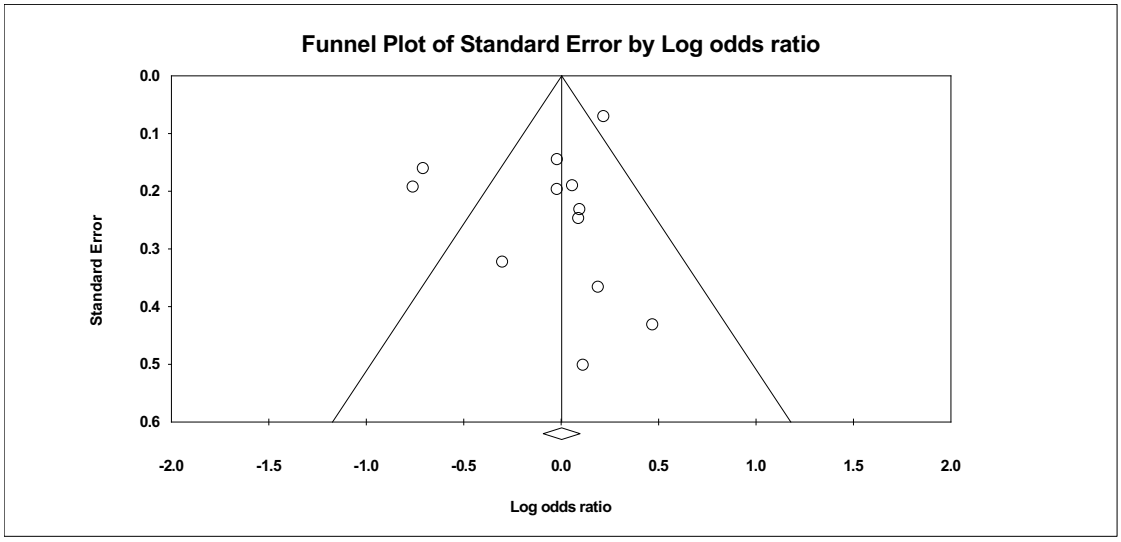
Supplementary Figure 10: Forest plot of the association between low birth weight and subsequent IBD diagnosis: cohort studies (I^2 42.67%)



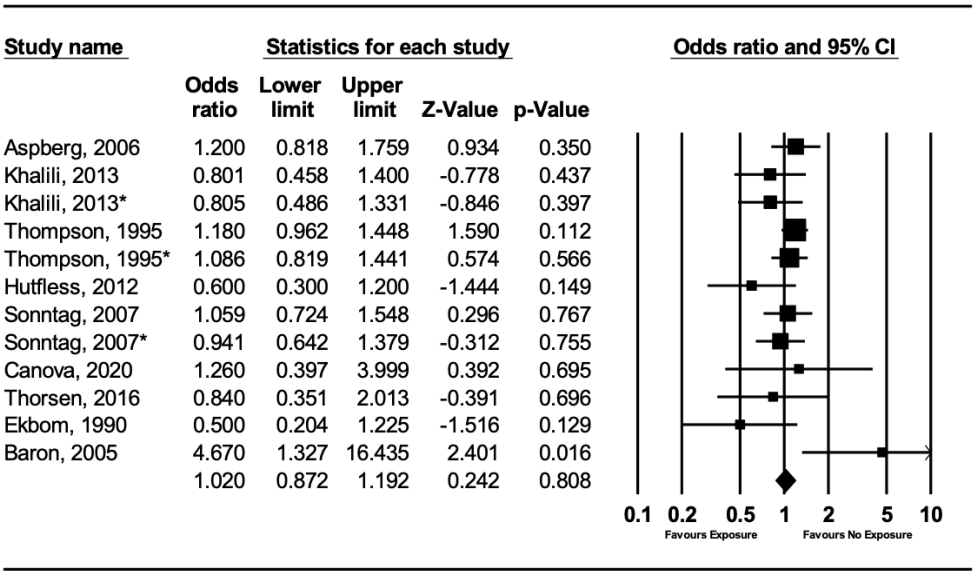
Supplementary Figure 11: Forest plot of the association between low birth weight and subsequent IBD diagnosis: case-control studies (I^2 73.39%)



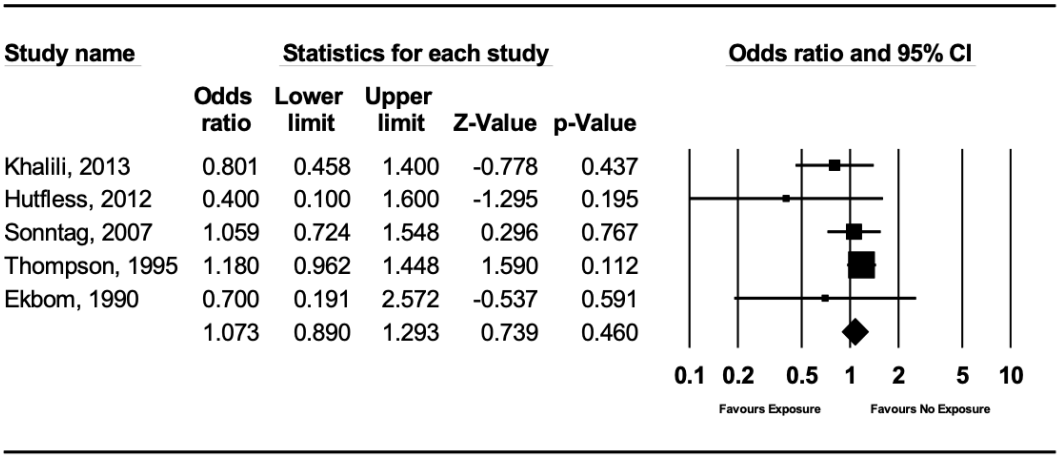
Supplementary Figure 12: Funnel plot to assess publication bias in studies on the association between low birth weight and subsequent IBD diagnosis (Egger's 2-sided p-value 0.353)



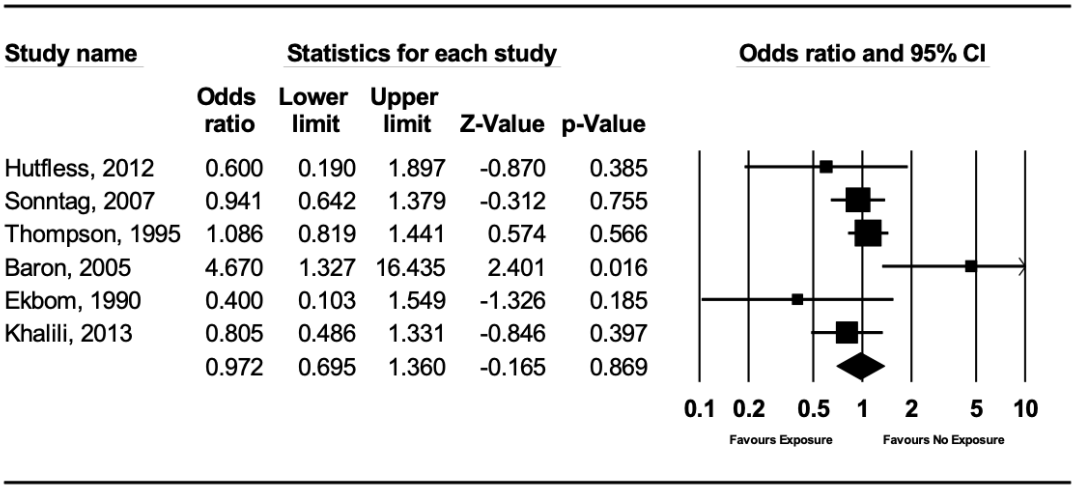
Supplementary Figure 13: Forest plot of the association between premature birth and subsequent IBD diagnosis (I^2 26.47%)



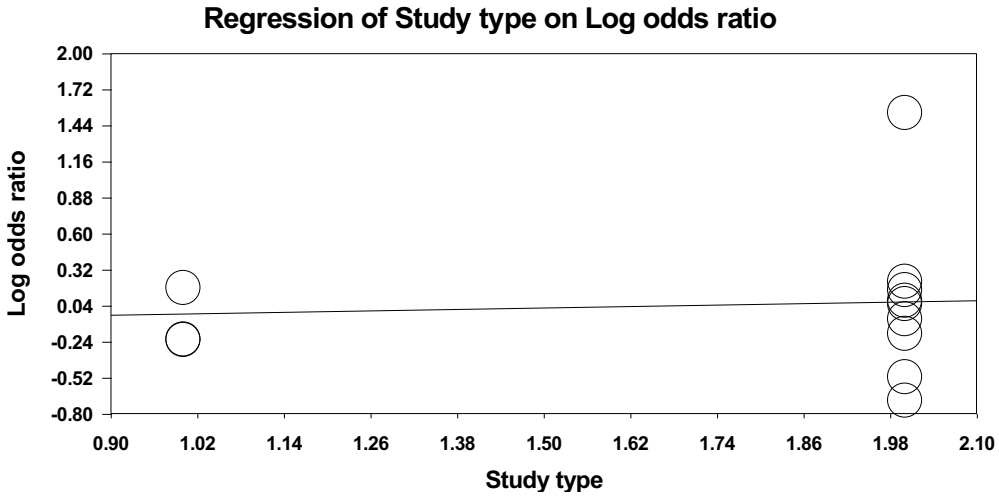
Supplementary Figure 14: Forest plot of the association between premature birth and subsequent CD diagnosis (I^2 5.33%)



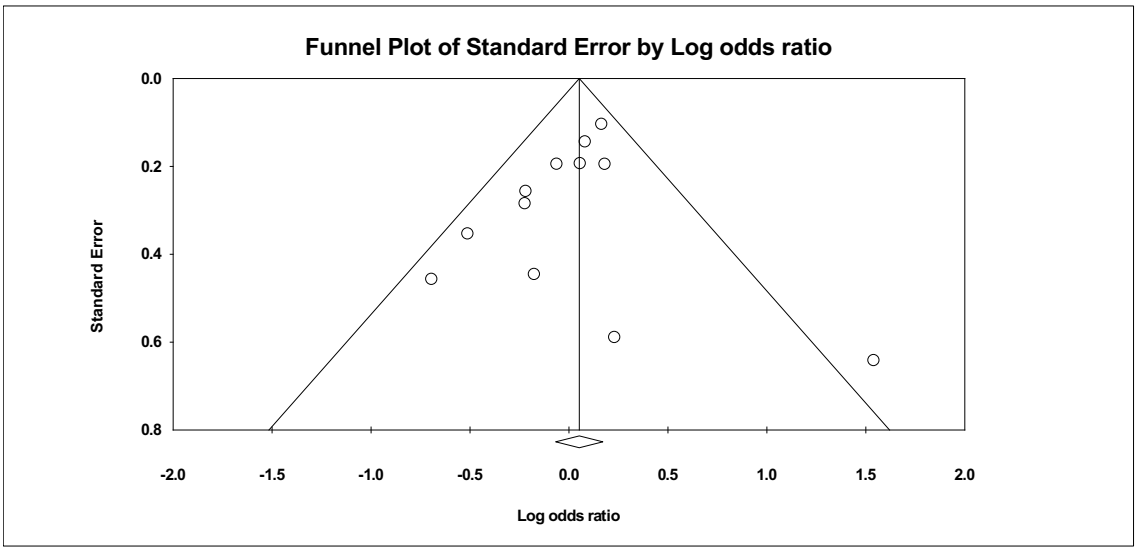
Supplementary Figure 15: Forest plot of the association between premature birth and subsequent UC diagnosis (I^2 46.91%)



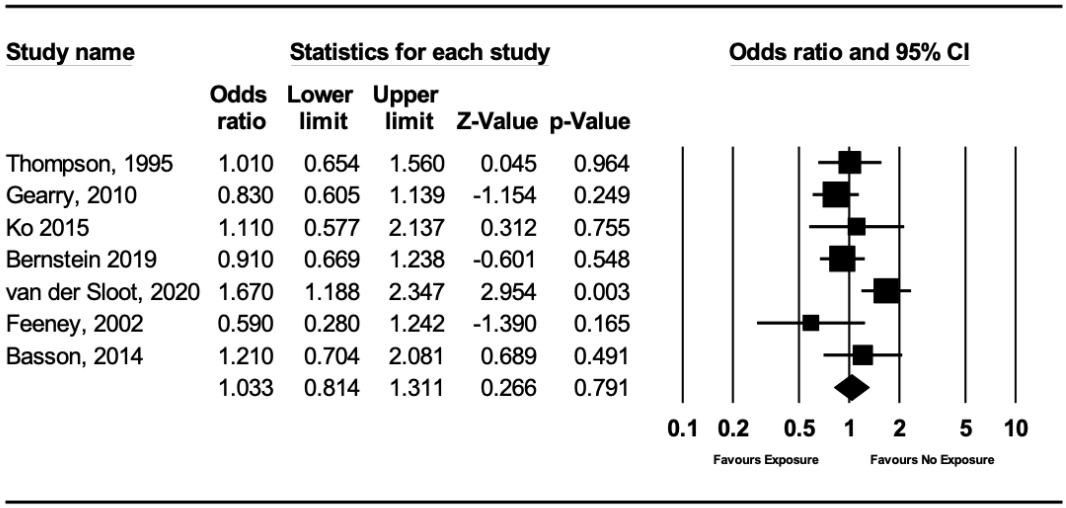
Supplementary Figure 16: Meta-regression of cohort vs case-control studies on the association between premature birth and subsequent IBD diagnosis (P value of slope 0.538)



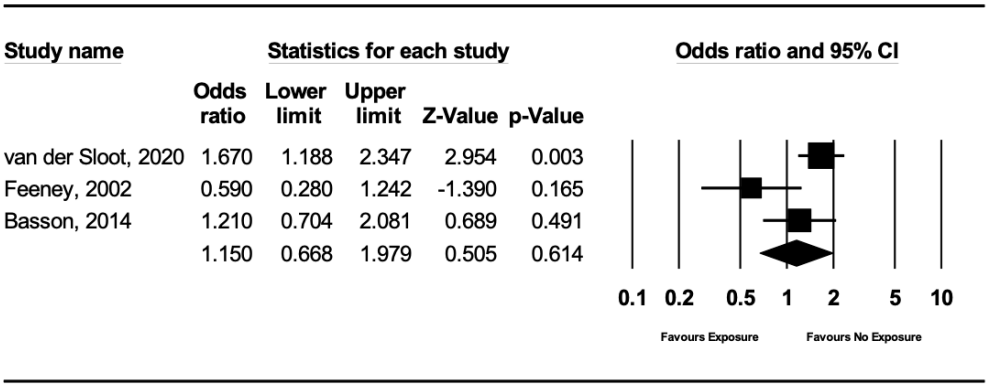
Supplementary Figure 17: Funnel plot to assess publication bias in studies on the association between premature birth and subsequent IBD diagnosis (Egger's 2-sided p-value 0.41)



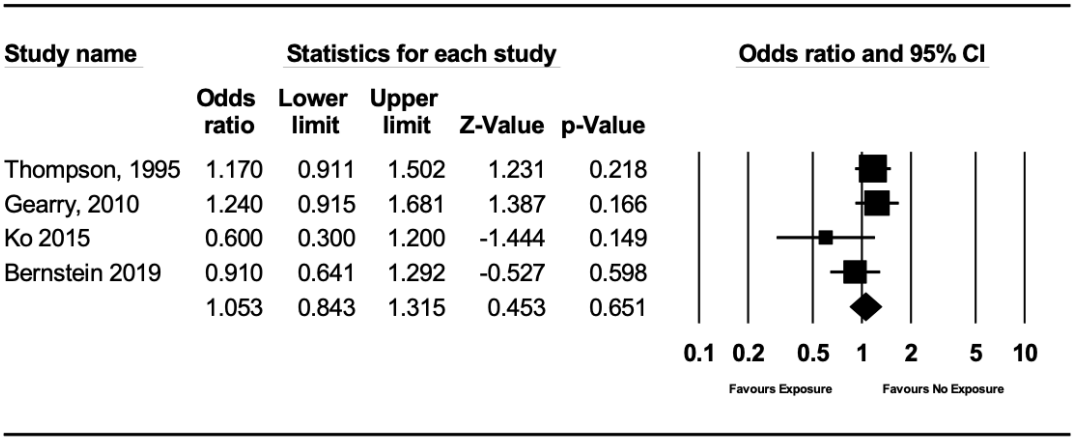
Supplementary Figure 18: Forest plot of the association between rural vs urban living and subsequent IBD diagnosis (I^2 52.76%)



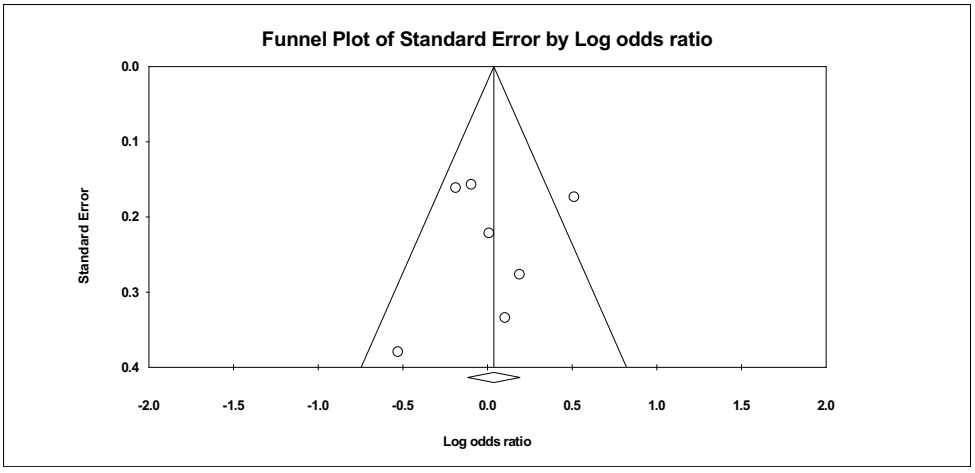
Supplementary Figure 19: Forest plot of the association between rural vs urban living and subsequent CD diagnosis (I^2 68.81%)



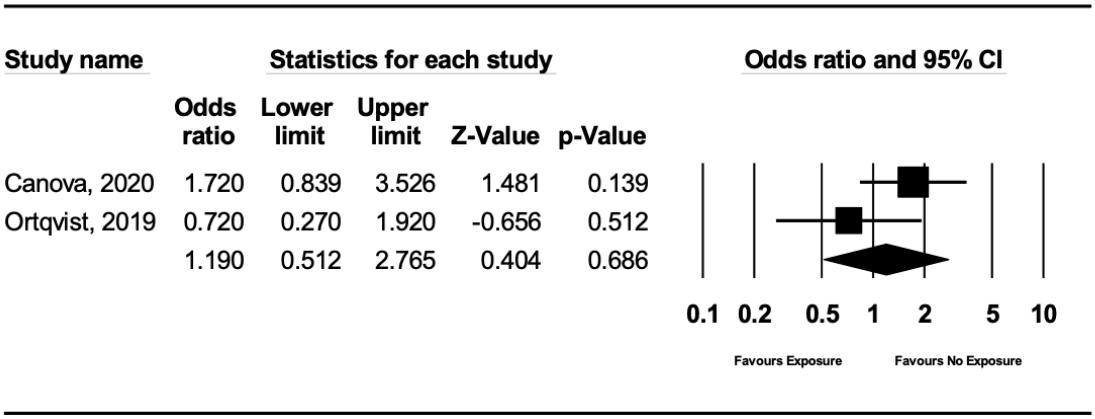
Supplementary Figure 20: Forest plot of the association between rural vs urban living and subsequent UC diagnosis (I^2 38.33%)



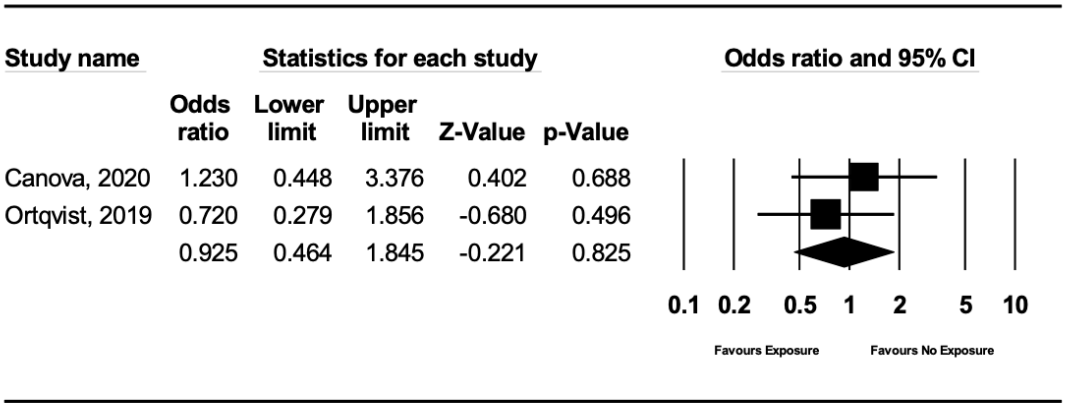
Supplementary Figure 21: Funnel plot to assess publication bias in studies on the association between rural vs urban and subsequent IBD diagnosis



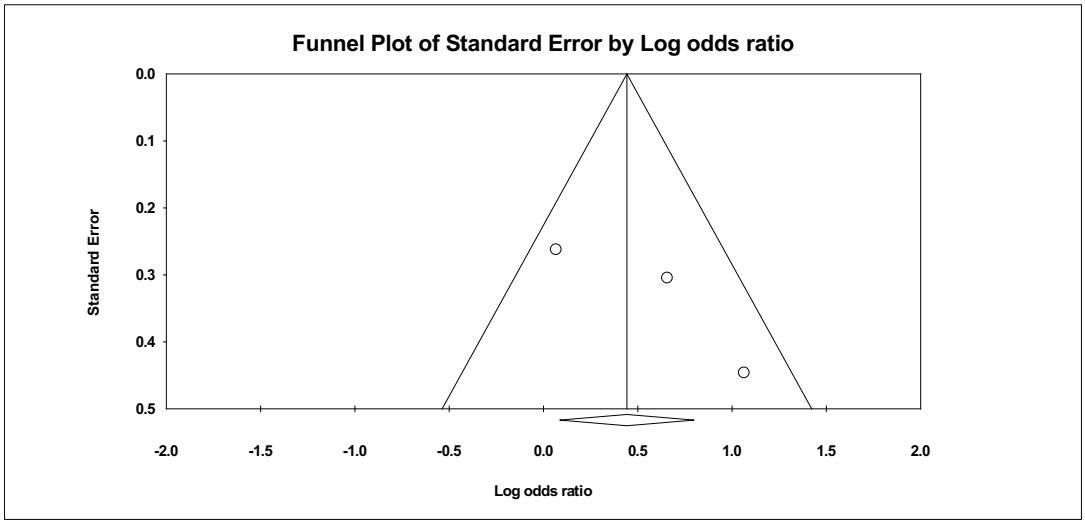
Supplementary Figure 22: Forest plot of the association between antibiotic exposure during infancy and subsequent CD diagnosis (I^2 49.29%)



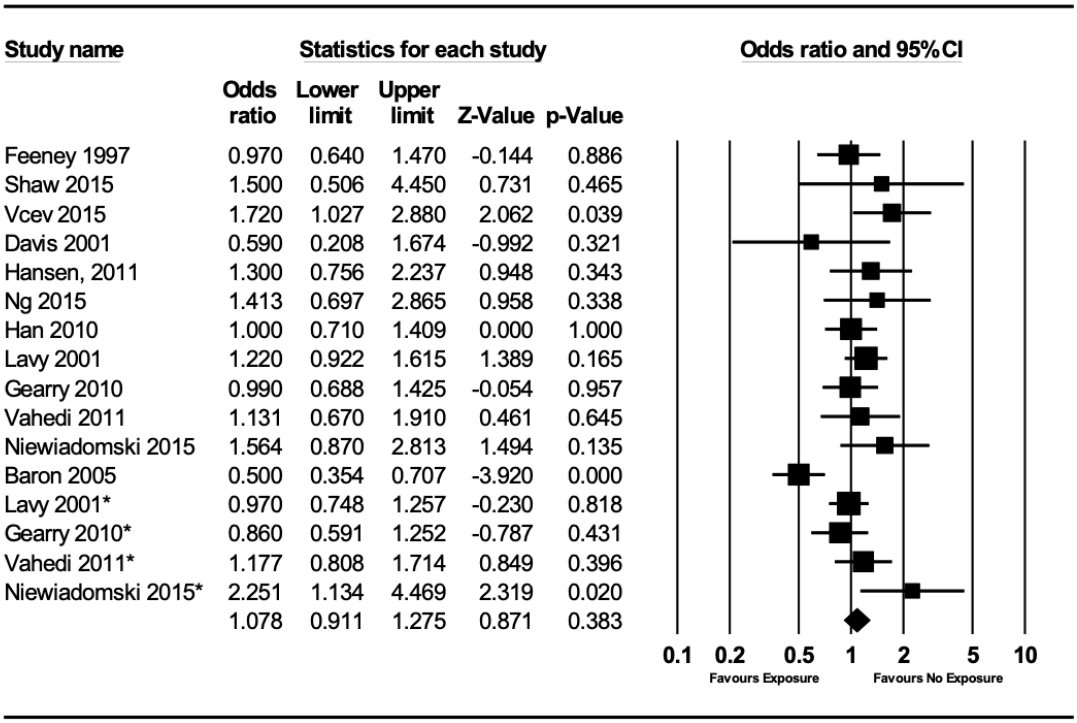
Supplementary Figure 23: Forest plot of the association between antibiotic exposure during infancy and subsequent UC diagnosis (I^2 44.82%)



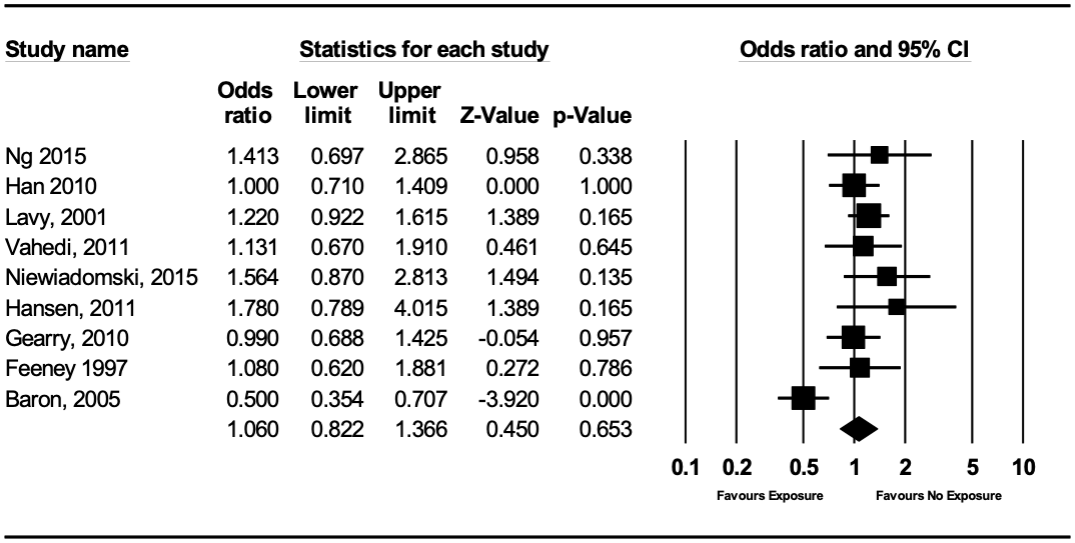
Supplementary Figure 24: Funnel plot to assess publication bias in studies on the association between antibiotic exposure during infancy and subsequent IBD diagnosis



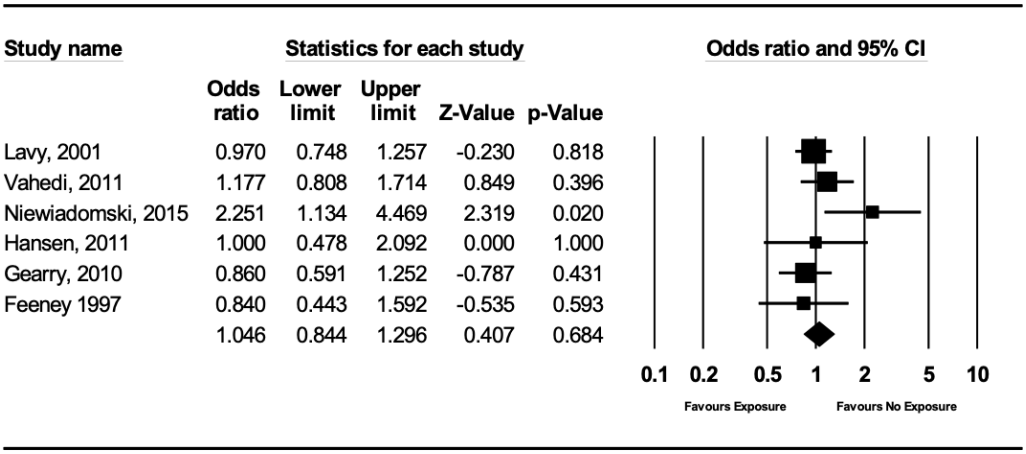
Supplementary Figure 25: Forest plot of the association between measles vaccine and subsequent IBD diagnosis (I^2 55.52%)



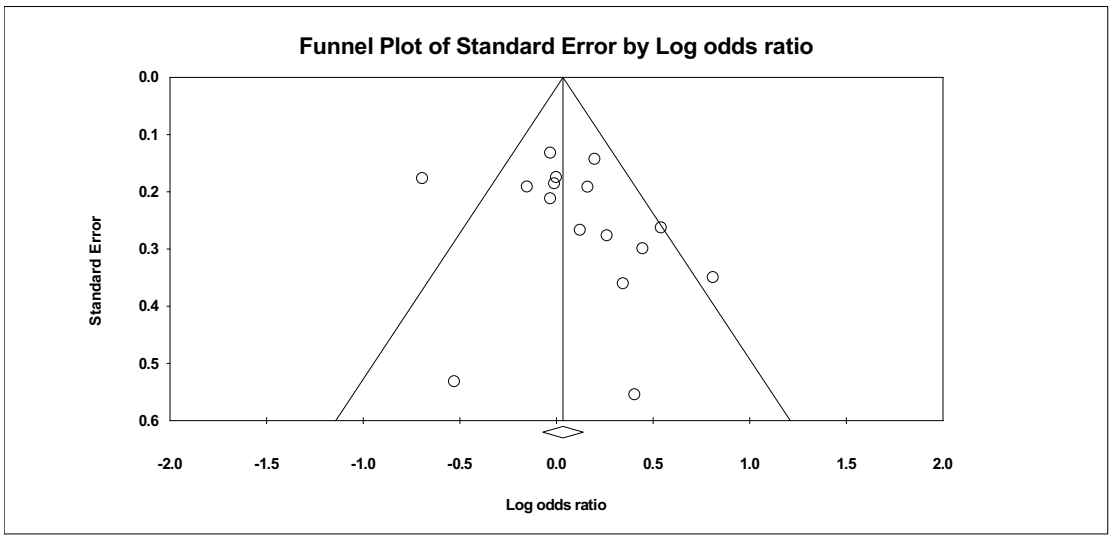
Supplementary Figure 26: Forest plot of the association between measles vaccine and subsequent CD diagnosis (I^2 64.69%)



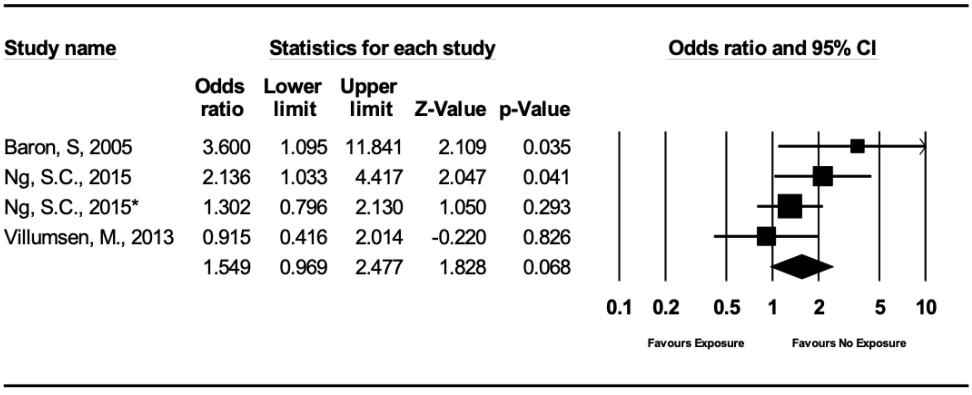
Supplementary Figure 27: Forest plot of the association between measles vaccine and subsequent UC diagnosis (I^2 28.2%)



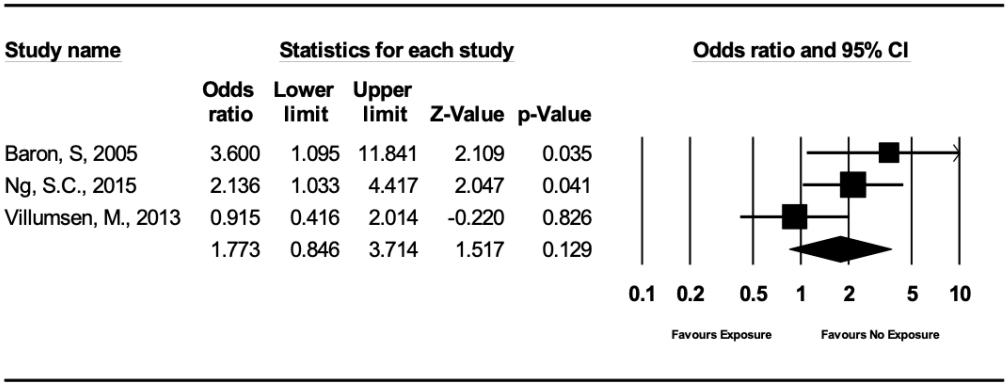
Supplementary Figure 28: Funnel plot to assess publication bias in studies on the association between measles vaccine and subsequent IBD diagnosis (Egger's 2-sided p-value = 0.206)



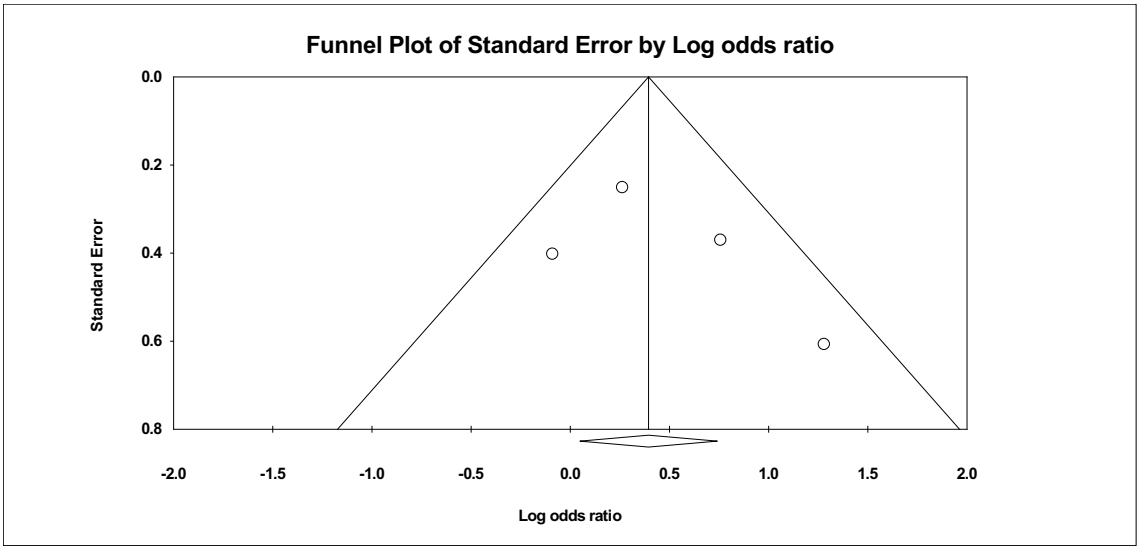
Supplementary Figure 29: Forest plot of the association between BCG vaccine and subsequent IBD diagnosis (I^2 37.58%)



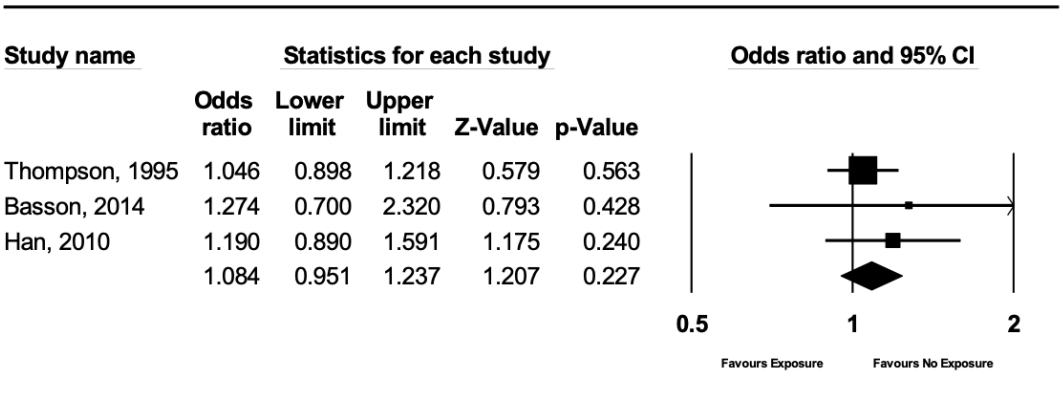
Supplementary Figure 30: Forest plot of the association between BCG vaccine and subsequent CD diagnosis (I^2 53.17%)



Supplementary Figure 31: Funnel plot to assess publication bias in studies on the association between BCG vaccine and subsequent IBD diagnosis



Supplementary Figure 32: Forest plot of the association between passive exposure to tobacco smoke and subsequent CD diagnosis (I^2 64.16%)



Supplementary Figure 33: Funnel plot to assess publication bias in studies on the association between passive exposure to tobacco smoke and subsequent CD diagnosis