

表4. 既往歴とMCTD発症のリスク、SLE発症のリスク

既往歴	MCTD 年齢補正 OR(95%CI)	九州SLE 年齢補正 OR(95%CI)	北海道SLE 年齢補正 OR(95%CI)
喘息	1.01 (0.36-2.82)	0.26 (0.03-2.06)	0.75 (0.21-2.74)
関節リウマチ	1.32 (0.05-32.11)	34.95 (1.95-625.09)	3.83 (0.29-50.99)
アレルギー	0.35 (0.120-1.03)	0.36 (0.11-1.23)	0.90 (0.39-2.07)
蕁麻疹	0.62 (0.23-1.67)	0.56 (0.20-1.56)	1.22 (0.51-2.91)
膠原病	35.73 (1.95-655.34)	12.82 (1.45-113.02)	1.71 (0.07-41.28)
アトピー性皮膚炎	0.33 (0.08-1.45)	0.46 (0.15-1.46)	0.81 (0.27-2.39)

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分担研究報告書

クローン病の発症関連要因に関する検討（文献的考察と研究計画）

井手悠一郎、乾未来、大藤さとこ、廣田良夫
（大阪市立大学大学院医学研究科公衆衛生学）

研究要旨

クローン病の発症関連要因を検討するための多施設共同・症例対照研究の実施に向けて、検討すべき要因を明確化するため、クローン病の関連要因に関する系統的レビューを行った。

「潰瘍性大腸炎のリスク因子に関する症例対照研究」と同様のプロトコールにて、症例対照研究を実施する。調査協力機関は、「難治性炎症性腸管障害に関する調査研究」班の班員所属施設である。症例は調査施設において初めてクローン病の診断を受けた患者、対照は症例と同じ施設に通院している他疾患患者のうち、各症例に対し性・年齢（5歳階級）が対応する患者2人を選出する。調査施設に過度の負担を掛けることなく、長期的に対象者の登録を継続できるよう、各調査施設において症例と対照のセットを1年間に2セット登録する。生活習慣、生活環境、既往歴などに関する情報収集は、クローン病のリスク因子に関する系統的レビューに基づき作成した自記式質問票を使用して行う。このほか、クローン病の発症時期、病状などの臨床情報については、臨床調査個人票を用いて、情報収集を行う予定である。

系統的レビューの結果、検討すべき主たる要因として、母乳栄養、小児期の感染曝露歴、喫煙、虫垂手術を含む既往歴、炎症性腸疾患の家族歴、経口避妊薬、各種食事因子などが考えられた。

A. 研究目的

クローン病の有病率および罹患率は、南欧、アジア諸国、および発展途上国において低いとされていたが、近年、上昇傾向を認めている。本邦においても、クローン病の公費補助の申請数が大幅に増加し、平成20年度には2万9千人に達する（図1）。その背景には環境因子をはじめとする、新しいリスク因子の出現が示唆されている。そこで、クローン病の増加を説明する要因を検討するため、症例対照研究を計画した。

B. 研究方法

2010年4月23日時点でPubMedに登録されていた過去10年間の論文から検索を行った。キーワードは、crohn disease AND risk AND (cross-sectional study OR case-control study OR cohort study) NOT polymorphism とし、English, Humans で制限した。

該当した論文のうち、Title および Abstract から考慮すべきものを選定し、内容を一定のフォームにまとめた。

C. 研究結果

該当論文は 598 編であった。このうち、①クローン病患者における他疾患（大腸がん、PSC、胆石、骨粗鬆症、骨折等）のリスク因子を検討したもの 85 編、②病理所見、画像所見、診断、症状、治療、予後に関するもの 380 編、③遺伝子に関する研究 54 編、④医療費に関する研究 1 編、⑤記述疫学 10 編、⑥クローン病の研究ではないもの 2 編」を除外し、最終的に論文 66 編をレビューの対象とした¹⁾⁻⁶⁶⁾。

このうちクローン病の発症関連要因を検討した研究は、コホート研究が 12 編、症例対照研究が 35 編であった。

高リスク因子として、高年齢、白人、ユダヤ民族、炎症性腸疾患 (IBD) 家族歴、急性感染性胃腸炎既往、虫垂切除、アレルギー性鼻炎、小児期の受動喫煙、現在喫煙、経口避妊薬、高年齢での出産、西洋食、コーヒー、菓子類摂取、肉類摂取、脂肪摂取などが報告されていた (Table 1-1)。

低リスク因子として、母乳栄養、MMR ワクチン接種、過去喫煙、野菜/果物摂取、乳製品摂取などが報告されていた (Table 1-1)。

一方、母乳栄養、虫垂切除、現在喫煙、過去喫煙、飲酒、measles vaccination (MMR、MCV vaccine を含む)、乳製品摂取、肉類摂取に関しては、関連を認めなかったという報告も数編認められた (Table 1-1)。

性別、運動頻度、兄弟数、居住地域 (urban vs rural)、膀胱炎、小児期の感染曝露を示す因子、左利き、通園歴、水泳、引越し、ペット飼育などとクローン病との関連は明らかではなかった (Table 1-1)。

クローン病の増悪と関連を示す因子とし

ては、卵、肉類をはじめとする蛋白質摂取、脂肪摂取が挙げられていた (Table 1-2)。

D. 考察

近年、世界の各国でクローン病の有病率、罹患率が上昇している。その原因をさぐべくさまざまな研究が実施されているが、クローン病発症のリスク因子を検討した疫学研究は非常に少ない。

複数の研究で、高リスク因子として炎症性腸疾患の家族歴、虫垂切除歴、現在喫煙、低リスク因子として過去喫煙が挙げられている。その他の因子に関しては、報告数が限られていたり、一貫した結果が得られていないため、未だ確立されたものではない。また、「socioeconomic status が高いほど炎症性腸疾患の発症リスクが高い」という研究結果より「衛生仮説：感染の曝露歴は炎症性腸疾患の発症を低下させる」が提唱されているが、一貫した結論は得られていない。

従って、今まで示唆されてきた関連因子を検証し、かつ新たな関連因子を模索するためには、新たな研究を実施する必要がある。また、クローン病のリスク因子を明らかにすることは、近年の患者増を検討する際のエビデンスとなろう。

E. 結論

クローン病の患者増の要因を検討すべく、症例対照研究を計画している。過去の研究報告のレビューにより、検討すべき主たる要因として、母乳栄養、小児期の感染曝露歴、喫煙、飲酒、虫垂手術を含む既往歴、炎症性腸疾患の家族歴、経口避妊薬、各種食事因子などが考えられた。

これらの項目は、現在実施中の潰瘍性大

腸炎のリスク因子に関する症例対照研究にて使用している調査票に含まれており、同一プロトコール、調査票により検討可能である。

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- F. 研究発表
1. 論文発表 なし
2. 学会発表 なし
- G. 知的財産権の出願・登録状況（予定を含む）
1. 特許取得 なし
2. 実用新案登録 なし
3. その他 なし

クローン病医療受給者証交付件数の推移

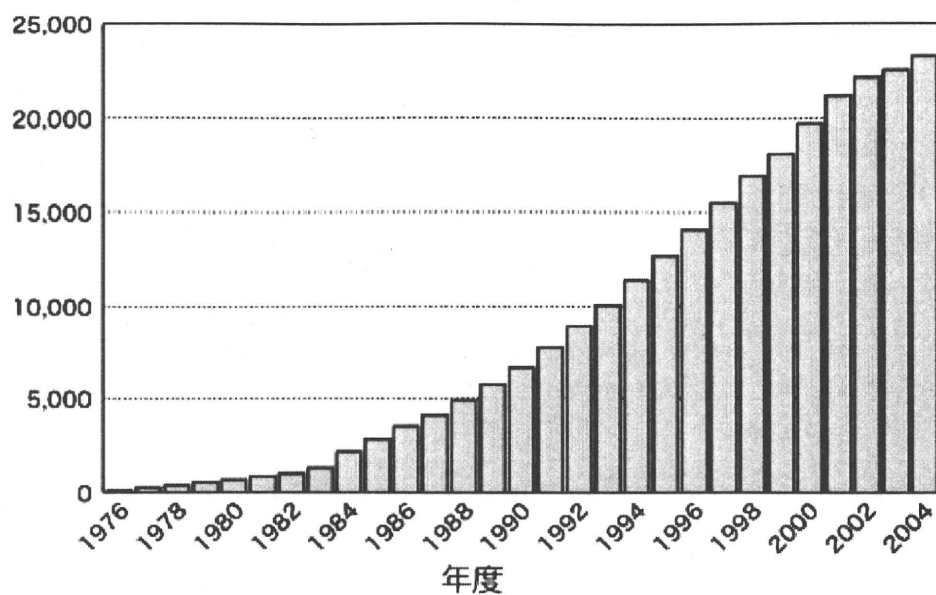


図 1

Table 1-1. Previous studies in relation to associated factors for Crohn disease.

Ref. Authors/Year/Country	Study Design/Follow-up period	Subjects (M: male, F: female)	Case definition	Mean (or median) age (M: male, F: female)	Main results Risk factors	Association	Protective factors	Association	Variables indicated no association	Association
1 Lian L. et al. 2008 US	Case-control study 2001-2007	CD of the pouch 42 (M: 18, F: 24) All jejunitis patients 231 (M: 128, F: 103)	prevalent	44.3	Active smoking	OR=5.64 (1.98-16.1)		OR=5.64 (1.98-16.1)	Gender (Male) Duration of the pouch (< 1 year) Thrombocytosis (< 450x10 ⁹ /L) EIM (PSC, eye disease, skin lesion thromboembolic, joint) WBC (< 10.2x10 ⁹ /L) Hemoglobin Age at diagnosis (per 10 years) Family history of BD Smoking	OR=1.23 (0.8-2.51) OR=1.05 (0.89-1.12) OR=0.87 (0.38-1.97) OR=0.86 (0.31-1.4) OR=1.01 (0.93-1.10) OR=0.98 (0.73-1.31) OR=0.83 (0.29-1.71) OR=1.14 (0.70-1.87)
2 Dasopoulos T. et al. 2009 US	Population based case-control study 2003-2007	Cases: 183 (M: 92, F: 91) Control: 143 (M: 55, F: 88) 7/5. History of BD	prevalent	Case-38.2 Control-38.6	ASCA (per 25 units) Disease duration (per 10 years) Self-reported Crohn's disease Parental ulcerative colitis	OR=1.13 (1.01-1.27) OR=1.01 (0.91-1.12) OR=1.97 (1.84-2.12) SIB=2.35	CD in offspring was associated with parental UC			
3 Tammi K. et al. 2009 Sweden	Population based case-control study 1984-2004	77 inflammatory disease patients-172/242	prevalent	patients-50 controls-49	Increment of 1 1st-degree relative with CD Increment of 2 1st-degree relative with CD Increment of 3 1st-degree relative with CD 2 additional antibody tested positive (anti-ASCA, anti-AMA) 3 additional antibodies tested positive (anti-ASCA, anti-AMA, ALCA, ALCA, ALCA, ALCA)	OR=1.53 (1.27-1.84) OR=2.33 (1.62-3.37) OR=3.57 (2.08-6.19) OR=1.53 (1.18-1.98) OR=6.65 (3.81-11.30) OR=17.14 (7.73-38.01)				
4 Joossens M. et al. 2009 Belgium and France	Population based case-control study 54 months follow up	CD patients-162 (M: 71, F: 91) Healthy Control-219 (M: 103, F: 116)	incidence	patients with CD - 44.9 1st degree healthy relatives-3.1 healthy control-30.5	ASCA prevalence	CD-43.9%, HR=38.3% Control-22%, p<0.05 CD-72%, HR=34% Control-4%, p<0.001				
5 Standaert-Viase A. et al. 2009 Belgium and France	Hospital based case-control study	Multiple families Patients with CD-129 (M: 56, F: 73) Healthy relatives-113 (M: 46, F: 73) Cases-10 families Healthy Control-76 (M: 32, F: 44)	prevalent		Appendectomy	The risk of CD was increased during the first year following an appendectomy. OR=2.08 (1.01-4.29)				OR=22%, HR=19%, Control=21%, p=0.045
6 Fujita T. 2009 Japan	Meta-Analysis of Kaplan 16 case-control and 3 cohort studies 2004-2008	Case-199 (M: 71, F: 99) Control-207 (M: 110, F: 97)	prevalent	Case-34 Control-38	Exposure to refrigerator at home since birth	OR=2.41 (1.18-4.87) OR=2.64 (1.29-5.39) OR=2.6 (1.4-5.0) OR=3.3 (1.5-8.1) OR=3.4 (1.3-9.3)				OR: not presented OR: not presented OR: not presented OR=1.90 (0.95-3.78)
7 Meelozzen F. et al. 2008 Japan	Hospital based case-control study 2005-2008	Case-37 (M: 17, F: 90) Control-41 (M: 23, F: 18) Matched for age and ethnicity	incidence	Case-12.8 Control-11.4	Fish/Shellfish Fats/Oils Sweets and Sugar Confectionery Fast Foods	OR=1.46 (1.07-1.99) OR=1.73 (1.10-2.71) OR=1.47 (1.04-2.07) OR=1.46 (1.05-2.08) OR=1.67 (1.17-2.39) OR=1.95 (1.45-2.82) OR=1.75 (1.38-2.21) OR=2.08 (1.19-3.84)				OR: not presented
8 Hayden MB. et al. 2008 US	Hospital based case-control study 2005-2008	Case-238 Control-478 Matched for sex, abnormality, married, SES, maternal age, interventional birth, urban, and year of birth	incidence		Living in urban areas Married mother SEIFA index (SES) vs 985.78 and under 1057.79 and over Maternal age vs 12-25 29-32 Mode of delivery vs Vaginal cephalic Ectopic cesarean Forceps/vacuum Interventional delivery vs Spontaneous cephalic/breech Infant congenital abnormality	OR=1.00 (0.79-1.27) OR=0.96 (0.74-1.25) OR=1.12 (0.78-1.61) 1010.77-1057.79 OR=1.06 (0.75-1.50) OR=1.29 (0.89-1.85) OR=1.41 (0.97-2.05) OR=0.48 (0.17-1.22) OR=0.89 (0.75-1.30) OR=0.89 (0.13-6.73) 27w and under 28w - 35w Weight at birth vs 2500-3995g <1500g 1500-2499g 2500-3995g 4000g and over OR=0.65 (0.16-2.62) OR=0.76 (0.39-1.48) OR=0.87 (0.39-1.28) OR=1.50 (0.89-2.29) OR=1.24 (0.46-3.36) OR=0.64 (0.09-4.58) OR=1.04 (0.07-1.62) OR=0.38 (0.17-1.19) OR: not presented				OR=1.00 (0.79-1.27) OR=0.96 (0.74-1.25) OR=1.12 (0.78-1.61) 1010.77-1057.79 OR=1.06 (0.75-1.50) OR=1.29 (0.89-1.85) OR=1.41 (0.97-2.05) OR=0.48 (0.17-1.22) OR=0.89 (0.75-1.30) OR=0.89 (0.13-6.73) 27w and under 28w - 35w Weight at birth vs 2500-3995g <1500g 1500-2499g 2500-3995g 4000g and over OR=0.65 (0.16-2.62) OR=0.76 (0.39-1.48) OR=0.87 (0.39-1.28) OR=1.50 (0.89-2.29) OR=1.24 (0.46-3.36) OR=0.64 (0.09-4.58) OR=1.04 (0.07-1.62) OR=0.38 (0.17-1.19) OR: not presented

Table 1-1 (Continued)

Ref. Author(s)/Year/Counter No.	Study Design/Year/Follow-up period	Subjects (M: male, F: female)	Case Definition	Mean (or median) age (F: female)	Main results	Association	Protective factors	Association	Variables indicated no association	Association
14 Hildebrandt H, et al. 2006 Sweden	Population based case-control study followed both 1970 and 1997	Case-1098 Control- 6530 Total- 9648 (M: 4487, F: 4151) Matched for maternal age	prevalent		Pneumonia Infant respiratory distress syndrome (IRDS)	OR=3.38 (1.79-7.06) OR= 11.95 (1.09-131.82)	Immigration vs 0-10% 11-62%		Appendicitis Sepsis Cytitis Cholecystitis Obstet. med.	OR=1.19 (0.14-10.22) OR=1.28 (0.37-4.46) OR: not presented OR=1.19 (0.14-10.22) OR=1.61 (0.85-2.82)
15 Lowe AM, et al. 2008 Canada	Cohort study 1993-2002	Total-21,172 CD patients F/M ratio- 0.34 (0 yrs -14 yrs) - 1.77 (15-65 yrs)	Incidence	Age vs 0-19 20-39 40-49 50-59 60-69 70-74 Gender (female) Incidence 5 enteric diseases (100,000/pers-yr) vs 7-14 15-100 9 enteric diseases: campylobacteriosis, salmonellosis, shigellosis, giardiasis, cryptosporidiosis, Jewish descent vs 0-1 (%) Iron pH	IRR=2.64 (2.34-2.93) IRR=1.86 (1.73-2.00) IRR=1.50 (1.36-1.64) IRR=1.95 (1.86-2.27) IRR=1.23 (1.04-1.82) IRR=1.18 (1.00-1.40)			Aboriginal vs 31.8 % 0-9.33% 0-1.5% Osteoporosis (28days preception/year) vs 0-3 >4 Jewish descent vs 0-1% 2-19%	IRR=1.02 (0.88-1.22) IRR=0.95 (0.79-1.15) IRR=1.05 (0.85-1.17) IRR=1.02 (0.87-1.21)	
16 Aarnot G, et al. 2008 Norway	Cohort study 1990-1993 3 years follow-up	762 IBD patients (M/F ratio- N/A)	Incidence		Prior exposure to infectious gastroenteritis Heredity Previous IBD diagnosis	IRR=1.70 (1.30-2.21) RR= 1.22 (1.00-1.48) RR= 1.02 (1.00-1.04)	Single	OR=0.82 (0.69-0.97)	Aluminum Californ bacteria Turbidity Color More than high school education	RR= 0.87 (0.77-1.23) RR= 0.89 (0.98-1.0) RR= 1.05 (0.98-1.09) RR= 1.00 (1.00-1.00) OR=1.05 (0.82-1.21)
17 Porter CK, et al. 2006 US	Nested Cohort Study 1989-2006	Cases-107 patients-1007 (M: 622, F: 485) all IBD patients-3019 (M: 2488, F: 531) Controls 11,648 (M: 9640, F: 2008) Matched for time of diagnosis.	Incidence	Cases-107 patients-1007 (M: 622, F: 485) all IBD patients-3019 (M: 2488, F: 531) Controls 11,648 (M: 9640, F: 2008) Matched for time of diagnosis.		OR=1.34 (1.17-2.04) RR= 1.22 (1.00-1.48) OR=1.71 (1.39-11.53)				
18 Nguyen GG, et al. 2008 US	Observational study Data from NIS b/w 1988 and 2004	18 Samples of All Patients- 527,187 (M: 41%, F: 59%) All CD Patients-73,187 (M: 42%, F: 58%)	prevalent	All Patients- CD patients- all IBD patients- Controls- 34	Age (per 10yr) Health insurance vs private Medicaid Bowel resective surgery	OR=2.06 (1.79-2.24) OR= 2.57 (1.63-4.04) OR= 4.82 (3.74-6.21)			Gender (Female) Health insurance vs private Medicare Self-pay Controlled for: Region vs Northeast Midwest South West Urban Large hospital vs small/medium MAP	OR=0.85 (0.74-1.21) OR= 1.33 (0.87-1.98) OR= 1.56 (0.97-3.65) OR= 1.86 (0.79-3.68) OR=0.86 (0.57-1.11) OR=0.78 (0.39-1.07) OR=0.72 (0.48-1.09) OR=0.82 (0.77-1.28) 23 case-control studies reported non-significant positive association, 1 case-control study didn't support the association.
19 Weidell LA, et al. 2008 Canada	Systematic review of 80 case-control studies 1 cross sectional study 4 descriptive studies				MAP reported significant positive association.	-23 case control studies reported significant positive association.	MAP	14 case-control studies didn't detect MAP		
21 Rendon K, et al. 2008 Germany	Hospital based case-control study 2007	Case-133 Control- 148	prevalent	all subjects between 6 and 10 years	Allergic rhinitis	Correlated significantly w/ CD OR: not presented	Contact with farm animals during the 1st year of life Regular contact with cats	Protective of IBD OR: not presented OR=0.2 (0.1-0.5) M: OR= 0.2 (0.1-0.5) F: OR= 0.3 (0.1-0.9)		M: OR=1.8 (0.7-4.4)
22 D'Souza S, et al. 2007 Canada	Population and hospital based case-control study	Case-149 (M: 91, F: 58) Control-251 (M:120, F: 131)	prevalent	Control- 12.3	Western (meat, fried foods, fast foods, snacks and desserts)	F: OR=4.7 (1.6-14.2)	Prudent (vegetables, fruits, eggs, olive oil, dairy products, fish, shellfish, and nuts)		Western (meat, fried foods, fast foods, snacks and desserts)	
23 Malmqvist G, et al. 2007/US	Cohort study 1987-2005	IFAA patients-238 (M:137, F:101) CD patients-16 Control-286038-222	Incidence	CD patients- non CD	Family history of CD anti-Saccharomyces cerevisiae(PSCA) IgA	HR= 8.4 (2.99-24.1) HR=3.14 (1.1-9.81)				HR=3.32 (0.85-17.2)
24 Ernst A, et al. 2007 Denmark	Hospital based case-control study 2004-2005	Case-125 patients-111 (M:62, F:296) US patients-985 (M: 289, F:296) Healthy Control - 1736 (M: 412, F: 384) Matched for ethnicity	prevalent	Case- CD Control- healthy	two CARD 15 mutations one CARD 15 mutation 100% CD mutation bial involvement Ever smoker	OR=22.2 95% CI: not presented OR=1.8 95% CI: not presented OR=2.8 (1.4-5.0) OR=3.6 95%CI: not presented OR= 1.8 (1.4-2.3)			OR: not presented	

Table 1-1. (Continued)

Ref. No.	Author(s)/Year/Country	Study Design/Year/Follow-up period	Subjects (M: male, F: female)	Case definition	Mean (or median) age (M: male, F: female) (years)	Main results	Association	Protective factors	Association	Variables indicated no association	Association
25	Rudin K, et al. 2007 Germany	Hospital based case-control study 2005-2006	Case CD patients-444 (M:272, F:172) UC patients-304 (M:158, F:146) Healthy Control - 1481 (M: 711, F: 770)	prevalent	CD patients-14 UC patients-13.7 Healthy control-13.1 Living in urban area	Risks with BD Male gender Allergic rhinitis Living in urban area	OR=5.3 (3.1-8.0) OR=1.6 (1.3-2.0) OR=1.6 (1.3-2.1) OR=1.5 (1.1-2.0)	Birth weight of <2500g Maternal smoking during pregnancy 2 or more older siblings Farm animals	OR=0.5 (0.4-0.7) OR=0.5 (0.4-0.8) OR=0.6 (0.4-0.8) OR=0.5 (0.3-0.9)	Pets Nutrition other than breast milk at <5 months	OR=1.0 (0.8-1.3) OR=0.5 (0.7-1.3)
26	Anne DK, et al. 2007 Canada	Hospital based case-control study 2003-2006	CD patients-130 (M: 77, F: 53) Control-122 (M: 90, F: 112)	incidence	Case-14.2 Control-12.2	Retinol (IU) Vitamin D (IU) Nicotin (mg)	OR=2.92 (1.26-4.90) OR=2.77 (1.12-6.92) OR=2.86 (1.05-7.93)	Fruits Nuts LCH- ω -3 (mg) SFA (mg) Monounsatur (mg) Potassium (mg)	OR=0.48 (0.25-0.95) OR=0.16 (0.04-0.95) OR=0.25 (0.08-0.71) OR=0.25 (0.08-0.71) OR=0.36 (0.10-0.86) OR=0.23 (0.09-0.64)	Vegetables Dairy Animal fats (g) SFA (mg) Carbohydrates (g) Fish Protein (g) SFA (Saturated fatty acids) (g) MUFA (g) Cholesterol (mg) ω -3 fatty acids (mg) Cholesterol (mg) MUFA (g) Carbohydrates w/o fiber (g) Carotene (IU) Vitamin A (IU) Vitamin E (mg) Vitamin C (mg) Thiamine (B1) (mg) Riboflavin (B2) (mg) Pyridoxin (B6) (mg) Coccolactone (mg) Calcium (mg) Iron (mg) Phosphorus (mg) Zinc (mg) Sodium (mg) Copper (mg)	OR=0.89 (0.33-1.44) OR=0.86 (0.42-1.78) OR=1.31 (0.59-2.93) OR=0.48 (0.19-1.18) OR=0.38 (0.09-1.63) OR=0.46 (0.20-1.06) OR=0.45 (0.13-1.50) OR=1.81 (0.39-8.61) OR=2.41 (0.72-8.07) OR=2.38 (0.84-6.71) OR=0.50 (0.19-1.38) OR=1.42 (0.51-3.92) OR=0.48 (0.19-1.18) OR=0.80 (0.35-1.84) OR=1.12 (0.39-3.28) OR=0.55 (0.28-1.18) OR=0.88 (0.38-2.04) OR=1.16 (0.48-2.81) OR=1.13 (0.52-2.44) OR=1.71 (0.89-3.34) OR=0.93 (0.42-1.95) OR=0.88 (0.38-2.04) OR=1.89 (0.84-4.27) OR=0.83 (0.25-1.59) OR=2.50 (0.90-6.94) OR=0.36 (0.11-1.12) OR=2.53 (0.96-6.69) OR=0.88 (0.29-3.62) OR=1.04 (0.44-2.47)
27	Kugabhasan S, et al. 2007 US	General remarks				Environmental factors—Smoking, diet, drug, SES stress, the enteric flora, altered intestinal permeability and CARD 15/NOD2, distal large intestine, Crohn's disease, Homolog 5, and interleukin-23 receptor(IL-23R) Microbial factors—Limonocycogenes, Citrazonatis, E. coli, Cytomegalovirus, S. cerevisiae, and M. avium-intracellulare Immune factors—human β -defensin(HBD)-2, HBD-3/Tr-17 cells, and Th 1 response Other, cancer factors— Intestinalulcerocolitis(MUC2)	ORs: not presented				
28	Keplan GG, et al. 2007 Sweden and Denmark	Cohort study 1984-2004	Sweden- 443,761 (M:198,136, F:245,623) Denmark- 265,592 (M:113,336, F:152,256)	incidence	Age group 1-4 5-9	Time since appendectomy (yrs) 10-14 14-19 20	SIR=6.89 (7.88-8.44) SIR=3.16 (2.58-3.99) SIR=1.88 (1.89-2.05) SIR=1.23 (1.12-1.39)				SIR=1.03 (0.91-1.17) SIR=0.98 (0.84-1.15) SIR=1.09 (0.93-1.27)
29	Tuvin JA, et al. 2008 US	Companion study 1977-2004 1999-2002	CD sporadic-218 CD familial-303	incidence	Age group sporadic vs familial 16-24: 42 vs 100 25-44: 106 vs 97 45-64: 39 vs 21 >65: 4 vs 6	Current smoking (vs general population)	Age group of CD familial 25-44 OR=1.9 (1.28-2.96)				Age group of CD sporadic 18-24 OR=0.6 (0.28-1.33)
30	Alfhouse MS, et al. 2009 Scotland	Observational Study 2000-2005	Ex-smokers of CD patients-53 (M:27, F:26) Non-smokers of CD patients-177 (M:72, F:105) Current smoker of CD patients-178 (M:56, F:120)	prevalent	Age group 20-34.5 35-42.5 43-48.7 Current-48.7	Smoking habit was associated with age at diagnosis, time to new onset yrs, at with disease location, Smoking habit Current smokers had less colonic disease than non-smokers or ex-smokers.					

Table 1-1. (Continued)

Ref. Authors/Year/Country	Study Design/Year/Follow-up period	Subjects (M: male, F: female)	Case definition	Mean (or median) age (M: male, F: female)	Main results	Association	Protective factors	Association	Variables indicated no association	Association
31 Abubakar, J, et al. 2006 UK	Hospital based case-control study 1995-2004	Case-218 (M: 94, F: 124) Control-412 (M: 309, F: 503)	prevalent	Case-42 Control-51	Ever smoking Smoking during the year of interest Smoking frequency (cigarettes/day) 1-9 10-19 20 Family history of CD Mean dietary intake Meat	OR=1.32 (1.34-2.48) OR=1.27 (1.14-1.41) OR=1.89 (1.14-3.08) OR=2.88 (1.86-4.44) OR=2.36 (1.46-3.82) OR= 7.13 (3.97-15.08) OR=1.40 (1.17-1.67)	Mean dietary intake Pasteurized milk Fruits Presence of a water filter Vacationing abroad	OR=0.82 (0.89-0.87) OR=0.78 (0.87-0.82) OR=0.54 (0.32-0.82) OR=0.56 (0.40-0.79)	Gender (Female) Mean water consumption Unbottled water Bottled water Mean dietary intake Dairy products Fish Cod liver oil Appendectomy Waste supply vs Private Public Dishwashing method vs Machine Hand Vacationing on a farm Visiting a farm	OR=1.22 (0.89-1.87) OR=1.01 (0.80-1.15) OR=0.99 (0.89-1.09) OR=0.96 (0.85-1.07) OR=1.01 (0.91-1.13) OR=0.99 (0.88-1.01) OR=1.29 (0.80-2.08) OR=1.60 (0.44-5.74) OR=1.27 (0.87-1.84) OR=0.83 (0.81-1.42) OR=1.02 (0.86-1.34) OR=1.03 (0.89-1.07)
32 Mehd SS, et al. 2006 US	Hospital based case-control study	Case-377 (M: 136, F: 239) Control-384 (M: 113, F: 140)	prevalent	Case-48 Control-50	Prenatal smoke exposure Passive smoke exposure during childhood Father Other Active smoke exposure during childhood ≤10 yrs ≤15 yrs	OR=1.72 (1.1-2.71) OR=1.47 (1.00-2.16) OR=1.94 (1.38-2.34) OR=3.85 (1.44-11.2) OR=3.06 (1.79-5.38)			Passive smoke exposure during childhood Mother Active smoke exposure during childhood ≤20 yrs	OR=1.29 (0.89-1.86) OR=0.75 (0.39-1.44)
33 Burt SR, et al. 2006 Canada	Population based case-control study 2002	Case-232 (M: 91, F: 141) Control-336 (M: 91, F: 245)	prevalent	Case-38.7 Control-38.9	CARD 15 vs wild type 1 mutant allele 2 mutant alleles Positive family history of BD Smoking ex-smoker current smoker Race and Ethnicity vs White, non-Jewish Jewish	OR=3.24 (2.3-5.1) OR=40.0 (12-136) OR=6.2 (2.5-15.3) OR=1.7 (1.0-2.7) OR=3.0 (1.8-4.9) OR=18.5 (2.2-15.8)			Race and Ethnicity vs White, non-Jewish non-white	OR=0.6 (0.3-1.5)

Table 1-1. (Continued)

Ref./Author/Year/Country	Study Design/Year/Follow-up period	Subjects (M: male, F: female)	Case definition	Mean (or median) age (M: male, F: female) (years)	Main results Risk factors	Association	Protective factors	Association	Variables indicated no association	Association
34 Halverson J, et al. 2008 Sweden and Denmark	population based co-twin control	CD case: 102 (M: 41/F: 61) control: 289	prevalent	25	Total marker of infections and colonization before age at 20 recurrent gastrointestinal infections hospitalization for gastrointestinal infections smoking habits at diagnosis smoker	Di- and Monozygotic OR=5.3 (1.2-26) OR=12 (1.6-92) OR=23 (1.2-7.1)	Total Diet before diagnosis intake of fruit daily	Di- and Monozygotic OR=0.2 (0.1-0.9)	Total recurrent respiratory infections childhood respiratory infections tonsillitis cholecystectomy vacation traveling abroad antibiotics swimming in pool, sea, or river Diet before diagnosis intake of vegetables intake of eggs daily weekly intake of fruit weekly additional sugar on breakfast cereals additional sugar in coffee or tea physical activity before diagnosis mainly swimming in lakes additional sugar on porridge coffee, no. of cups per day 3+ 1-2 smoking habits at diagnosis ex-smoker appendectomy before age 20 oral contraceptive use at diagnosis smoke of tea, different types of bread, soft drinks, juice, fast food and cereals	Di- and Monozygotic OR: not presented OR: not presented OR: not presented OR: not presented OR: not presented OR: not presented OR: not presented OR=0.4 (0.1-2.6) OR=0.8 (0.4-1.7) OR=0.4 (0.1-1.4) OR: not presented OR: not presented OR: not presented OR=1.1 (0.4-2.7) OR=1.2 (0.6-2.6) OR=2.1 (0.7-6.0) OR=1.6 (0.6-4.7) OR=2.7 (0.7-10) OR=2.0 (0.4-11) OR=1.3 (0.4-3.3) OR: not presented
					Total recurrent respiratory infections childhood infections, tonsillitis, vaccinations, cholecystectomy, traveling abroad, and antibiotics mainly swimming in lakes swimming in pool, sea, or river Diet before diagnosis intake of fruit daily weekly intake of vegetables intake of eggs weekly additional sugar on porridge additional sugar on breakfast cereals additional sugar in coffee or tea swimming in pool, sea, or river intake of different types of bread, cereals, soft drinks, juice, and fast food smoking habits at diagnosis smoker ex-smoker appendectomy before age 20 oral contraceptive use at diagnosis physical activity before diagnosis	Monozygotic pairs OR: not presented	Total recurrent respiratory infections childhood infections, tonsillitis, vaccinations, cholecystectomy, traveling abroad, and antibiotics mainly swimming in lakes swimming in pool, sea, or river Diet before diagnosis intake of fruit daily weekly intake of vegetables intake of eggs weekly additional sugar on porridge additional sugar on breakfast cereals additional sugar in coffee or tea swimming in pool, sea, or river intake of different types of bread, cereals, soft drinks, juice, and fast food smoking habits at diagnosis smoker ex-smoker appendectomy before age 20 oral contraceptive use at diagnosis physical activity before diagnosis	Monozygotic pairs OR: not presented OR=2.0 (0.4-11) OR: not presented OR=0.2 (0.01-3.0) OR=0.7 (0.1-9.0) OR: not presented OR=0.8 (0.2-3.4) OR=1.2 (0.4-3.9) OR: not presented OR: not presented OR: not presented OR: not presented OR=0.7 (0.1-40) OR=0.5 (0.04-5.5) OR=1.4 (0.2-14) OR: not presented		

Table 1-1. (Continued)

Ref. Authors/Year/Country	Study Design/Year/Follow-up period	Subjects (M: male, F: female)	Case definition	Mean (or median) age (M: male, F: female)	Main results	Association	Protective factors	Association	Variables indicated no association	Association
36 Bernstein CN, et al. 2008 Canada	population based case-control	CD case: 384 control: 432 frequency matching with age, sex, geographic residence	prevalence		demographics and household residents first disease relatives with IBD childhood food experiences frequency of eating pork as a child (medium vs low) smoking, malleic acid, and OCP use ever smoking smoking now user of acetaminophen regularly ever user of other pain killer regularly ever number of years of OCP use between: 15-19 20-24 25-29 30-34 35-39 15-39	OR=5.66 (1.91-16.0) OR=3.02 (1.87-4.88) OR=2.48 (1.40-4.40) OR=1.78 (1.32-2.41) OR=1.96 (1.36-2.78) OR=2.27 (1.87-3.11) OR=2.18 (1.52-3.11) OR=1.21 (1.04-1.42) OR=1.32 (1.05-1.61) OR=1.33 (1.05-1.61) OR=1.44 (1.11-1.88) OR=1.07 (1.03-1.11)	demographics and household residents first generation Canadian number of brothers (mean) birth order (mean) number of household residents prior to age 5 (mean) pet cats prior to age 5 at time of survey among those with pets, with cats childhood food experiences (medium vs low) lived on a farm ever (Y/N) frequency of drinking unpasteurized milk	OR=0.50 (0.31-0.83) OR=0.78 (0.87-0.80) OR=0.82 (0.70-0.96) OR=0.80 (0.82-0.88) OR=0.90 (0.83-0.97) OR=0.68 (0.50-0.92) OR=0.66 (0.46-0.95) OR=0.82 (0.46-0.85) OR=0.67 (0.49-0.91) OR=0.49 (0.33-0.65)	demographics and household residents urban vs rural ethnicity caucasian vs other born in developing world childhood food experiences main farm type (cattle) primary source of water: being any of well water, lake water or other non-tap source frequency of drinking diet soft drinks (medium vs low) frequency of eating chicken user of ASA regularly ever (Y/N) number of years of OCP use b/n 35-39	OR=1.05 (0.78-1.41) OR=1.56 (0.83-2.83) OR=0.22 (0.02-1.90) OR=0.69 (0.44-1.07) OR=0.77 (0.56-1.06) OR=0.68 (0.44-1.04) OR=1.42 (0.92-2.18) OR=0.91 (0.58-1.43) OR=0.98 (0.80-1.17) OR=1.26 (0.84-1.89)
37 Anon DK, et al. 2006 Canada	hospital based case-control	CD case: 194 control: 194	prevalent	12.28 8.63	day-care attendance (ever vs never) between birth & 6 months owning a pet (always vs never/sometimes) physician diagnosed childhood infections (ever vs never) 5-10 yr of age family history of IBD (Y/N)	OR=4.5 (1.4-13.7) OR=2.1 (1.3-3.3) OR=1.4 (0.9-2.1) OR=6.2 (1.9-20.5) OR=3.5 (1.8-6.8)	use of parental toilet (always vs never /sometimes)	OR=0.5 (0.3-0.7)	breastfeeding (ever vs never) birth to 6 months between 7 and 12 months beyond age 1 day-care attendance (ever vs never) between 7 months and 1 yr between age 1 and 3 yr age of pet water availability (always vs never/sometimes) bed sharing (always vs never/sometimes) owning a pet during pregnancy between birth and 5 yr of age between age 6 and 10 physician diagnosed childhood infections (ever vs never) 5 yr of age	OR=0.8 (0.5-1.3) OR=1.1 (0.7-1.9) OR=1.3 (0.7-2.6) OR=1.6 (0.5-5.1) OR=1.5 (0.8-2.8) OR=1.1 (0.6-1.8) OR=0.9 (0.5-1.8) OR=0.6 (0.3-1.5) OR=1.0 (0.4-2.4) OR=0.9 (0.5-1.6) OR=1.2 (0.7-2.2) OR=1.3 (0.6-2.9) OR=1.4 (0.9-2.1) OR=0.9 (0.6-1.5) OR=1.3 (0.7-2.4) OR=0.40 (0.15-1.08) OR=0.38 (0.05-3.10) OR=2.5 (0.48-12.85) OR=1.69 (0.54-5.24) OR=infinity (0-infinity) OR=1.34 (0.72-2.51) OR=0.51 (0.27-1.0) OR=5 (0.74-33.8) OR=infinity (0-infinity)
40 Frouzi F, et al. 2006 Iran	hospital based case-control	Case: 48 (M: 20/F: 28) Control: 194 (M:80/F: 104) match for age, sex	prevalent	38.02 39.02	appendectomy	OR=5.49 (1.41-21.34)			maternal smoking (ever vs never) 5 yr of age tomatoeateny current smoker NSAID user	OR=3.0 (0.9-10.1) OR=0.40 (0.15-1.08) OR=0.38 (0.05-3.10)
42 Van Kruiningen HJ, et al. 2005 Belgium	hospital based case-control	CD case: 74 (M: 32/F: 42) Unpaired family- 84 (M: 40/F: 44) Controls: 59 (M: 28/F: 31) match for family size, sex, ages of children	incidence	42 48	pericarditis diarrhea appendicitis skin disease uncooked pork unpasteurized milk unpasteurized cheeses smoked (ever)	OR=2.78 (1.28-6.13) OR=3.01 (1.37-6.81) OR=4.38 (1.0-19.4) OR=2.71 (1.05-7.0) OR=2.52 (1.06-6.0) OR=2.24 (1.10-4.58) OR=6.54 (1.94-22) OR=2.8 (1.47-5.34)	consumption of oats consumption of rye drank tap water contact with bird in the home contact with dog in the home contact with cat in the home	OR=0.34 (0.16-0.72) OR=0.38 (0.21-0.70) OR=0.20 (0.10-0.38) OR=0.34 (0.18-0.66) OR=0.45 (0.22-0.93) OR=0.48 (0.27-0.92) OR=0.13 (0.06-0.29)	hand, foot, mouth disease hepatitis A psoriasis uncooked beef consumption of bran beerput waste on garden drank well water	OR=1.69 (0.54-5.24) OR=infinity (0-infinity) OR=1.34 (0.72-2.51) OR=0.51 (0.27-1.0) OR=5 (0.74-33.8) OR=infinity (0-infinity)
43 Van Ranst M, et al. 2005 Belgium	hospital based case-control 1958-2002	CD patients: 1025 (M: 417/F: 608) Controls: 5125 match for birth year, sex	prevalent				born in June vs December	OR=0.64 (0.45-0.91)		
44 Klement E, et al. 2005 France	population based case-control 1988-1997	CD case: 222 (M: 130/F: 102) Controls: 222 (M: 130/F: 102) match for age, sex, living area	prevalent		breastfeeding	OR=2.1 (1.3-3.4)				
45 Franon S, et al. 2005 France	population based case-control 1988-1997	Case: 222 (M: 130/F: 102) Controls: 222 (M: 130/F: 102) match for age, sex, living area	prevalent		childhood factors familial history of IBD breast feeding eczema smallpox vaccination BCG vaccination poliomyelitis vaccination bedroom sharing	OR=4.6 (2.6-8.3) OR=1.6 (1.1-2.4) OR=2.9 (1.5-5.6) OR=2.1 (1-4.3) OR=2.8 (1.1-7.2) OR=2.6 (1.1-6.2) OR=1.6 (1-2.4)	Childhood factors MMR vaccination tap water consumption	OR=0.5 (0.35-0.9) OR=0.5 (0.3-0.8)		

Table 1-1. (Continued)

Ref. No.	Author/Year/Country	Study Design/Year/Follow-up period	Subjects (M, msk, F, female)	case definition	Mean (or median) age (M, msk, F, female)	Main results Risk factors	Association	Protective factors	Association	Variables indicated no association	Association
46	Skarmoto N, et al. 2005 Japan	hospital based case-control 2000-2001	CD cases: 126 (M: 91/F: 35) Controls: 211 (M: 135/F: 76) match for sex, age, hospital	prevalent	-	daily intake of food group (highest quartile vs lowest quartile) sugar and sweeteners confectioneries fats and oils fish and shellfish	OR=2.12 (1.06-4.17) OR=2.83 (1.38-5.83) OR=2.64 (1.29-5.39) OR=2.41 (1.19-4.89)	daily intake of food group (highest vs lowest quartile)	Association	Variables indicated no association daily intake of food group potatoes nuts and seeds pulses meats and poultry eggs milk and dairy products vegetables fruits mushrooms cereals alcoholic beverages rice breads noodles green-yellow vegetables other vegetables	OR=1.69 (0.85-3.35) OR=1.92 (0.94-3.91) OR=1.23 (0.63-2.40) OR=1.90 (0.95-3.78) OR=1.42 (0.72-2.83) OR=0.90 (0.24-1.09) OR=1.55 (0.76-3.17) OR=0.90 (0.38-1.86) OR=1.21 (0.62-2.62) OR=1.17 (0.57-2.47) OR=0.50 (0.23-1.11) OR=0.82 (0.33-1.88) OR=1.49 (0.76-2.66) OR=1.37 (0.71-2.66) OR=1.02 (0.50-2.11) OR=2.07 (0.98-4.37)
47	Garrido A, et al. 2004 Spain	population based case-control retrospective (1980-1996) prospective (1996-2003) meta-analysis	CD cases: 30 Controls: 7856	prevalent	32.3	daily nutrient intake (highest quartile vs lowest quartile) fat MUFA PUFA Vitamin E n-3 fatty acids n-6 fatty acids	OR=2.98 (1.35-5.90) OR=2.48 (1.23-5.03) OR=2.31 (1.12-4.79) OR=3.23 (1.52-6.88) OR=3.24 (1.52-6.88) OR=2.57 (1.24-5.32)	daily nutrient intake (highest vs lowest quartile)	OR=0.95 (0.81-0.99)	daily nutrient intake (highest quartile vs lowest quartile) protein carbohydrate calcium iron potassium Vitamin A Vitamin E retinol carotene Vitamin C SFA n-3 fatty acids magnesium zinc n-6/n-3	OR=2.06 (0.99-4.28) OR=0.53 (0.27-1.03) OR=0.67 (0.33-1.35) OR=1.86 (0.88-3.90) OR=0.72 (0.36-1.44) OR=1.49 (0.74-3.00) OR=1.06 (0.64-2.09) OR=1.89 (0.83-3.49) OR=0.87 (0.42-1.82) OR=1.46 (0.71-2.99) OR=1.11 (0.58-2.09) OR=0.71 (0.36-1.43) OR=1.28 (0.61-2.68) OR=0.73 (0.37-1.45)
48	Klement E, et al. 2004 Israel	hospital based case-control	CD cases: 90 (M: 57/F: 23) Community based control matched at a ratio of 3:1 by age and sex	prevalent	33.1	smoker ever-smoker (female)	OR=14.3 (3.1-66.6)	age	OR=0.45 (0.28-0.76) OR=0.55 (0.34-0.87) OR=0.67 (0.52-0.86)	breastfeeding (highest quality group) breastfeeding (highest and intermediate quality group) breastfeeding (all quality group)	OR=1.01 (0.74-1.37) OR=0.83 (0.36-2.00) OR=1.11 (0.94-1.07) OR=1.27 (0.96-1.68) OR=0.93 (0.69-1.26) OR=0.92 (0.65-1.31) OR=0.97 (0.62-1.51)
49	Lioung RW, et al. 2004 China	hospital based case-control	CD cases: 134 (M: 111/F: 172) by age and sex	prevalent	38.4 38.3	ever-smoker (female)	OR=7.56 (2.25-25.41)	breastfeeding (highest quality group) breastfeeding (highest and intermediate quality group) breastfeeding (all quality group)	OR=0.45 (0.28-0.76) OR=0.55 (0.34-0.87) OR=0.67 (0.52-0.86)	Variables indicated no association 1st-degree family member with IBD birth in non-Western nation father (male vs male) skin reaction drinking water source lived on dairy/beef farm	OR=1.01 (0.74-1.37) OR=0.83 (0.36-2.00) OR=1.11 (0.94-1.07) OR=1.27 (0.96-1.68) OR=0.93 (0.69-1.26) OR=0.92 (0.65-1.31) OR=0.97 (0.62-1.51)
52	Barronstein CN, et al. 2004 US	population based case-control	CD cases: 134 (M: 111/F: 172) by age and sex 402 (M: 111/F: 291) siblings control: 138 (M: 55/F: 83) matched with age, gender, geography	prevalent	38.4 38.3	ever-smoker (female)	OR=7.56 (2.25-25.41)	breastfeeding (highest quality group) breastfeeding (highest and intermediate quality group) breastfeeding (all quality group)	OR=0.45 (0.28-0.76) OR=0.55 (0.34-0.87) OR=0.67 (0.52-0.86)	Variables indicated no association 1st-degree family member with IBD birth in non-Western nation father (male vs male) skin reaction drinking water source lived on dairy/beef farm	OR=1.01 (0.74-1.37) OR=0.83 (0.36-2.00) OR=1.11 (0.94-1.07) OR=1.27 (0.96-1.68) OR=0.93 (0.69-1.26) OR=0.92 (0.65-1.31) OR=0.97 (0.62-1.51)

Table 1-3. (Continued).

Ref. No.	Authors/Year/Country	Study Design/Year/Follow-up period	Subjects (M: male, F: female)	Case definition	Mean (or median) age (M: male, F: female)	Main results	Association	Protective factors	Association	Variables indicated no association	Association
53	Card T. et al. 2004 UK	population based case-control	CD case: 587 (M: 253/F: 334) control: 1480 (M: 642/F: 818)	prevalent	41.64 43.76	Risk factors all subjects smoker drugs other than antibiotics antibiotics drugs for nervous system disease oral contraceptive pills antibiotics tetracyclines metronidazole and tinidazole	OR=1.55 (1.22-1.96) OR=1.54 (1.38-1.70) OR=1.32 (1.05-1.65) OR=1.34 (1.08-1.66) OR=1.48 (1.00-2.17) OR=1.34 (1.01-1.77) OR=1.70 (1.05-2.75)	antibiotics	OR=0.86 (0.64-1.16) OR=1.28 (0.95-1.86) OR=0.84 (0.74-1.21) OR=1.10 (0.90-1.36) OR=1.18 (0.88-1.58) OR=0.96 (0.72-1.27) OR=1.16 (0.88-1.57) OR=0.96 (0.72-1.27) OR=1.16 (0.88-1.57)	all subjects smoking status unknown drugs for cardiovascular disease	OR=0.86 (0.64-1.16) OR=1.28 (0.95-1.86)
54	Saagrott V. et al. 2003 UK	meta-analysis 1979-1998	CD case: 1959 (M: 749/F: 1210)	incidence	-	No. of courses of antibiotics 1 vs no symptoms or gastrointestinal 2-5 vs no symptoms or gastrointestinal masses vaccination program Thompson et al (1995)	OR=1.57 (1.07-2.29) OR=1.50 (1.05-2.14) RR=3.01 (1.5-6.3)	No. of courses of antibiotics	OR=1.51 (0.82-2.76) RR=0.91 (0.5-1.4) RR=1.08 (0.6-1.9) RR=0.87 (0.3-1.6) RR=1.11 (0.3-4.7)	over 5 vs no symptoms or gastrointestinal drugs masses vaccination program Feeney et al (1997) Morris et al (2000) Davies et al (2001)	OR=1.51 (0.82-2.76) RR=0.91 (0.5-1.4) RR=1.08 (0.6-1.9) RR=0.87 (0.3-1.6) RR=1.11 (0.3-4.7)
55	Andersson RE. et al. 2003 Sweden	population based cohort 1984-1993	patients with appendectomy: 21218 (M: 10476/F: 10543) control: 21218 matched with age at operation, sex, township of residence	incidence	-	total perforated appendicitis mesenteric lymphadenitis nonspecific abdominal pain other diagnosis men only nonspecific abdominal pain other diagnosis women only perforated appendicitis mesenteric lymphadenitis nonspecific abdominal pain other diagnosis sex (F/M)	HR=2.02 (1.43-2.86) HR=2.11 (1.50-2.97) HR=2.32 (1.79-3.56) HR=3.18 (2.24-4.53) HR=2.18 (1.06-4.54) HR=4.58 (2.42-8.60) HR=2.48 (1.59-3.91) HR=1.42 (1.08-1.85) HR=2.23 (1.51-3.31) HR=2.37 (1.59-3.52) HR=2.54 (1.68-3.89) OR=1.19 (1.14-1.23)	total men only women only	HR=2.22 (0.95-1.60) HR=1.65 (0.95-2.90) HR=1.04 (0.74-1.45) HR=1.45 (0.68-3.02)	nonperforated appendicitis men only perforated appendicitis mesenteric lymphadenitis women only	HR=2.22 (0.95-1.60) HR=1.65 (0.95-2.90) HR=1.04 (0.74-1.45) HR=1.45 (0.68-3.02)
56	Montgomery SM. et al. 2002 Sweden	population based case-control 1984-1998	CD case: 12685 (M: 5976/F: 6692) control: 63035 (M: 32423/F: 30612)	prevalent	-	No. of younger siblings 2 vs 0 3+ vs 0 mother's age 31-35 vs 21-25 36-40 vs 21-25 41-45 vs 21-25 years to birth of younger sibling 0-5 yr	OR=0.92 (0.87-0.98) OR=0.90 (0.83-0.97) OR=0.92 (0.87-0.97) OR=0.92 (0.86-0.98) OR=0.82 (0.72-0.93) OR=0.87 (0.81-0.93)	No. of younger siblings 1 vs 0 No. of older siblings 1 vs 0 3+ vs 0 multiple birth (Y/N) mother's age under 21 vs 21-25 26-30 vs 21-25 46-51 vs 21-25 years to birth of younger sibling 3-4 yr 5-6 yr 7 yr or longer	OR=0.96 (0.92-1.00) OR=1.02 (0.97-1.06) OR=0.98 (0.92-1.04) OR=0.98 (0.91-1.06) OR=0.85 (0.82-1.11) OR=1.04 (0.97-1.12) OR=0.97 (0.92-1.02) OR=0.83 (0.53-1.46) OR=0.95 (0.88-1.00) OR=0.98 (0.92-1.06) OR=0.98 (0.91-1.05)	No. of younger siblings 1 vs 0 No. of older siblings 1 vs 0 3+ vs 0 multiple birth (Y/N) mother's age under 21 vs 21-25 26-30 vs 21-25 46-51 vs 21-25 years to birth of younger sibling 3-4 yr 5-6 yr 7 yr or longer	OR=0.96 (0.92-1.00) OR=1.02 (0.97-1.06) OR=0.98 (0.92-1.04) OR=0.98 (0.91-1.06) OR=0.85 (0.82-1.11) OR=1.04 (0.97-1.12) OR=0.97 (0.92-1.02) OR=0.83 (0.53-1.46) OR=0.95 (0.88-1.00) OR=0.98 (0.92-1.06) OR=0.98 (0.91-1.05)

Table 1-1. (Continued)

Ref. No.	Author(s)/Year/Country	Study Design/Year/Follow-up period	Subjects (M: male, F: female)	case definition	Mean (or median) age (M: male, F: female)	Main results	Association	Protective factors	Association	Variables indicated no association	Association
57	Frasch M, et al. 2002 US	population based case-control 1989-1996	CD case: 498 control: 2498 matched with age, sex, race	prevalent	-	Risk factors age at appendectomy 21-34 35-44 45-54 55+ time since appendectomy 1 yr 2-4 yr	OR=2.5 (2.0-3.3) OR=5.7 (3.5-9.6) OR=2.7 (1.5-4.9) OR=2.4 (1.4-4.3) OR=1.5 (1.0-2.4) OR=10.0 (5.5-18.3) OR=3.2 (2.1-4.9)			time since appendectomy 5-14 yr 15+ yr	OR=1.4 (0.9-2.1) OR=1.2 (0.5-2.5)
58	Kurra LM, et al. 2002 UK	population based case-control 1963-1999	GD case: 5023 (M: 2034/F: 2989) control: 74832 (M:381632/F: 367890)	prevalent	-	age in year at operation (<20) years from operation <1 1-4 age in year at operation (>20) years from operation <1 1-4 age in year at operation (all ages)	OR=1.02 (0.76-1.33) OR=7.16 (3.90-12.05) OR=1.92 (1.58-2.32) OR=7.31 (5.22-9.96) OR=2.12 (1.48-2.83) OR=1.51 (1.28-1.76)	tonsilllectomy		age in year at operation (<20) years from operation 1-4 25 age in year at operation (>20) years from operation 1-4 25 age in year at operation (all ages)	OR=1.02 (0.76-1.33) OR=1.07 (0.55-1.87) OR=0.71 (0.47-1.03) OR=0.85 (0.65-1.35) OR=1.16 (0.37-3.7)
59	Fenney MA, et al. 2002 UK	hospital based case-control	GD case: 139 control: 139 matched with sex, age	prevalent	-	medical history eczema under 10 years family characteristics childhood circumstances Frequent use of swimming pool	OR=2.81 (1.23-6.42)	medical history hepatitis A IgG status IgG status family characteristics	OR=0.18 (0.06-0.52)	medical history hepatitis A IgG status appendectomy under 17 years family characteristics one sibling two or more siblings no older siblings one older sibling two older siblings childhood circumstances person-to-room ratio in home social class 1 or 2 social class 3 (M) or (N) social class 4 or 5 attended nursery attended swimming pool no family car in childhood one family car in childhood no house moves one house moves OR=1.78 (0.79-4.01) urban environment out in the home dog in the home bird in the home resident in the home	OR=0.33 (0.44-1.95) OR=0.33 (0.16-1.73) OR=0.71 (0.18-2.77) OR=0.48 (0.11-2.01) OR=1.38 (0.37-5.20) OR=0.96 (0.25-3.65) OR=1.11 (0.48-6.16)

Table 1-1. (Continued).

Ref. Authors/Year/Country	Study Design/Year/Follow-up period	Subjects (M, male, F, female)	case definition	Mean (or median) age (M, male, F, female)	Main results Risk factors	Association	Protective factors	Association	Variables indicated no association	Association
60 Scilla B, et al. 2001 Spain	population based case-control 1992-1995	CD case: 103 (M: 61/F: 42) control: 103 (M: 61/F: 42) matched with age, sex, rural/urban habitat.	prevalent	34.9 35.5	smoker number of cigarettes 1-10 cigarettes per day 11-20 cigarettes per day women only contraceptives ex-smoker smoker number of cigarettes 1-10 cigarettes per day	OR=3.08 (1.58-6.05) OR=6.44 (1.91-21.73) OR=2.87 (1.28-6.44)	women only		ex-smoker number of cigarettes >20 cigarettes per day women only ex-smoker number of cigarettes 11-20 cigarettes per day >20 cigarettes per day appendectomy left handed	OR=1.40 (0.28-6.93) OR=3.72 (0.82-16.94) OR=1.24 (0.25-6.04) OR=1.09 (0.24-4.93) OR=2.04 (0.02-186.2) OR=1.56 (0.60-4.02) RR=2.13 (0.97-4.64)
61 Morris DL, et al. 2001 UK	population based birth cohort 1970-1996	left handed subjects: 1972 (M: 1046/F: 882) no left handed subjects: 19225 (M: 7534/F: 7938)	incidence	-	appendectomy (women) year of appendectomy 1977-1980 1981-1984 1985-1989 age at appendectomy < 20 y 20-39 y 40-59 y cause of appendectomy other appendiceal disease incidental appendectomy total	RR=2.47 (1.98-3.03) RR=2.03 (1.53-2.63) RR=3.12 (2.33-4.08) RR=5.65 (4.05-7.86)			age at appendectomy 60+ y cause of appendectomy performing appendicectomy	RR=1.27 (0.41-2.97) RR=0.96 (0.26-2.45)
62 Frisch M, et al. 2001 Denmark	population based cohort	underwent appendectomy: 154434 (M: 82411/F: 92023)	incidence	-		RR=1.97 (1.41-2.69) RR=4.05 (3.21-5.03) RR=3.15 (2.04-4.65) RR=2.48 (1.90-3.19) RR=3.67 (2.93-4.54) RR=2.88 (2.45-3.39)				
63 Davis RL, et al. 2001 US	population based case-control	CD case: 75 control: 432 (M: 224/F: 208) matched with sex, Health Maintenance Organization, birth year	prevalent	-					ever vaccination (vs unvaccinated) measles-mumps-rubella (MMR) vaccine measles-containing vaccine (MCV) vaccinated age (vs unvaccinated) MMR <12 MMR 12-18 MMR >18 MCV <12 MCV 12-18 MCV >18	OR=0.40 (0.09-2.00) OR=1.11 (0.26-4.69) OR=0.38 (0.05-2.86) OR=0.54 (0.10-3.07) OR=0.18 (0.03-1.21) OR=0.43 (0.05-3.94) OR=1.16 (0.24-5.53) OR=1.56 (0.25-9.92) RR=0.80 (0.3-1.9)
64 Morris DL, et al. 2000 UK	population based birth cohort 1970-1996	measles vaccinated: 7319	incidence	26					measles vaccinated age at 5 yr	

Table 1-2. Previous studies in relation to associated factors for celiac diseases

Ref. Authors/year/Country	Study Design/year/Follow-up period	Subjects (M: male, F: female)	case	Mean (or median) age (M: male, F: female)	Main results Risk factors	Association	Productive factors	Association	Variables indicated no association	Association
35 Nguyen GC, et al. 2006 US	hospital based comparison study	CD cases: 697 white: 510 African American: 81 Hispanic: 106	prevalent	All cases: 26.4 white: 26.6 African American: 25.9 Hispanic: 25.9	prevalence of fecal involvement current smoker prevalence of esophagogastrroduodenal disease for African American (vs white) prevalence of colorectal disease for African American (vs white) prevalence of perianal disease for African American (vs white) for Hispanic (vs white) prevalence of stricture disease (after 5 yr since diagnosis) for African America (vs white)	OR = 1.86 (1.1-3.1) OR = 2.3 (1.4-3.5) OR = 1.9 (1.1-3.4) OR = 1.7 (1.03-2.8) OR = 2.3 (1.8-4.6)	prevalence of fecal involvement for African American (vs white) diagnosed at age >40 yr prevalence of upper gastrointestinal involvement for African American (vs white) prevalence of fecal involvement gender family history of IBD	OR = 0.55 (0.35-0.96) OR = 0.40 (0.18-0.91) 25.8% vs 16.1% (p=0.05) OR: not presented OR: not presented	prevalence of esophagogastrroduodenal disease for Hispanic (vs white) prevalence of abdominal penetrating disease for African American (vs white) prevalence of upper gastrointestinal involvement for African American (vs white)	OR = 0.23 (0.05-1.0) OR = 0.55 (0.3-1.0) 25.8% vs 16.1% (p=0.05) OR: not presented OR: not presented
38 Coevae J, et al. 2006 France	hospital based retrospective cohort 9.6 yr 9.1 yr	non-symptomized CD cases: 1770 (M: 751/F: 1019) symptomized CD cases: 716 (M: 207/F: 515)	prevalent	32.1 27.5	intestinal stricture prior appendectomy fecal involvement prior appendectomy	HR = 1.24 (1.13-1.36) HR = 0.80 (0.74-0.86) HR = 1.73 (1.60-1.87)	perianal perforating prior appendectomy surgery young age prior appendectomy colonic involvement prior appendectomy	HR = 0.75 (0.68-0.83) HR = 0.80 (0.74-0.86) HR = 0.66 (0.62-0.71)		
41 Lakatos PL, et al. 2005 Hungary	hospital based cohort 8.4 yr	familial CD cases: 73 (M: 33/F: 40) sporadic CD cases: 491 (M: 245/F: 246)	prevalent	36.3 37.5	Presence of extraintestinal manifestations: female gender Isocolonic or colonic location familial disease smoking Need for antibiotic Isocolonic or colonic location non-inflammatory behavior	OR = 1.51 (1.05-2.16) OR = 2.47 (1.57-3.8) OR = 1.88 (1.13-3.12) OR = 1.55 (1.06-2.22) OR = 3.59 (2.22-5.81) OR = 1.43 (0.89-22.77)	Presence of extraintestinal manifestations: non-inflammatory behavior Need to restriction extraintestinal manifestation familial disease smoking female gender	OR = 1.36 (0.94-1.96) OR = 0.75 (0.49-1.15) OR = 0.71 (0.46-1.08) OR = 1.04 (0.69-1.57)		
50 Montgomery SM, et al. 2003 Sweden	population based comparison	CD patients: 4626 (M: 2250/F: 2376) pediatric onset: 1115 (M: 669/F: 446) adult onset: 3711 (M: 1581/F: 2130)	prevalent	-	pediatric onset for females mother's age 25-30 vs under 21 mother's age 31-35 vs under 21 mother's age 36-40 vs under 21 mother's age 41-45 vs under 21	OR = 2.08 (1.19-3.68) OR = 3.50 (1.85-6.68) OR = 3.02 (1.38-6.75) OR = 12.84 (3.63-43.98)	pediatric onset for females mother's age 21-25 vs under 21 mother's age 26-30 vs under 21 mother's age 31-35 vs under 21 mother's age 36-40 vs under 21 mother's age 41-45 vs under 21 father's age 21-25 vs under 21 father's age 26-30 vs under 21 father's age 31-35 vs under 21 father's age 36-40 vs under 21 father's age 41-45 vs under 21 not available vs under 21 pediatric onset for males mother's age 21-25 vs under 21 mother's age 26-30 vs under 21 mother's age 31-35 vs under 21 mother's age 36-40 vs under 21 mother's age 41-45 vs under 21 father's age 21-25 vs under 21 father's age 26-30 vs under 21 father's age 31-35 vs under 21 father's age 36-40 vs under 21 father's age 41-45 vs under 21 not available vs under 21	OR = 1.47 (0.85-2.37) OR = not presented OR = 1.24 (0.47-3.37) OR = 1.16 (0.43-3.15) OR = 0.95 (0.33-2.63) OR = 0.95 (0.28-2.46) OR = 0.87 (0.28-2.93) OR = 1.12 (0.25-4.99) OR = 1.24 (0.29-5.87)		
51 Coevae J, et al. 2004 France	hospital based comparison 1985-2002	CD cases: 885 (M: 234/F: 654) smoker: 422 (M: 152/F: 270) non-smoker: 268 (M: 92/F: 176)	prevalent	-	Left-sided colitis in females non-smoker vs smoker Paracitils in females non-smoker vs smoker	31% vs 15%, p<0.01 32% vs 46%, p<0.01				