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RESEARCH ARTICLE

Global smoking trends in inflammatory bowel disease: A systematic review of inception cohorts

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Abstract

Background and aims
The effect of smoking on the risk of developing inflammatory bowel diseases (IBD) may be heterogeneous across ethnicity and geography. Although trends in smoking for the general population are well described, it is unknown whether these can be extrapolated to the IBD cohort. Smoking prevalence trends specific to the global IBD cohort over time have not been previously reported. This is a systematic review of smoking prevalence specific to the IBD cohort across geography.

Methods
A systematic literature search was conducted on Medline and Embase from January 1st 1946 to April 5th 2018 to identify population-based studies assessing the prevalence of smoking at diagnosis in inception cohorts of Crohn’s disease (CD) or ulcerative colitis (UC). Studies that did not report smoking data from time of diagnosis or the year of IBD diagnosis were excluded. Prevalence of smoking in IBD was stratified by geography and across time.

Results
We identified 56 studies that were eligible for inclusion. Smoking prevalence data at diagnosis of CD and UC was collected from twenty and twenty-five countries respectively. Never-smokers in the newly diagnosed CD population in the West have increased over the last two decades, especially in the United Kingdom and Sweden; +26.6% and +11.2% respectively. Never-smokers at CD diagnosis in newly industrialised nations have decreased over the 1990s and 2000s; China (-19.36%). Never-smokers at UC diagnosis also decreased in
China; -15.4%. The former-smoker population at UC diagnosis in China is expanding; 11% (1990–2006) to 34% (2011–2013).

Conclusion
There has been a reduction in the prevalence of smoking in the IBD cohort in the West. This is not consistent globally. Although, smoking prevalence has decreased in the general population of newly industrialized nations, this remains an important risk factor with longer term outcomes awaiting translation in both UC and CD.

Introduction
Our group has extensively reported that inflammatory bowel diseases (IBD) have become a global challenge in the 21st century.[1–5] The rapidly accelerating incidence of both Crohn’s disease (CD) and ulcerative colitis (UC) in the newly industrialized countries in the East mirrors epidemiological patterns of IBD in the West more than 75 years ago.[2] The evolving epidemiology of IBD is thought to be associated with the industrialisation of society. The rise of IBD incidence in newly industrialised nations combined with reports of comparable rates of IBD in migrant and native populations in the West[6] support the theory that environmental triggers and Western lifestyle have an integral role in the pathogenesis of IBD. [3,4]

The dichotomous relationship between smoking and the development of IBD has been the subject of intense scrutiny and is a complex interplay of genetics, immunology and environment. In the West, smoking has been consistently reported as a risk factor for developing CD and adversely affects disease course[7–9], whereas former smokers and non-smokers are at increased risk of developing UC in comparison to current smokers.[10,11] In contrast, studies in non-Western populations have been unable to replicate this association between CD and smoking.[12] The interaction between smoking and the NOD-2 gene and their effect on the risk of CD has been postulated to be specific to the 1007 fs mutation and a negative association between NOD-2 mutation and smoking could be explained by their inverse relationship.[13]

An understanding of global smoking prevalence trends specific to the IBD cohort is required as the foundation for further investigation of the heterogeneous influence of this risk factor in IBD pathogenesis and disease course across different regions. In addition, this is increasingly important in light of the identification of smoking as a key risk factor for non-response to anti-TNF agents in patients with CD.[14] However, the global prevalence of smoking associated with IBD have not been collated and reported. We conducted a systematic review to assess the prevalence of smoking in all population based IBD inception cohort studies. We examined smoking prevalence specific to individual IBD cohorts across time and geography.

Materials and methods
Search strategy and selection criteria
This systematic review was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[15] A systematic literature search (S1 Table) was conducted on Medline (01 January 1946 to April 5th 2018) and Embase (01 January 1947 to April 5th 2018) for studies assessing the prevalence of smoking at diagnosis in inception IBD cohorts. All studies from our previous systematic review on IBD epidemiology[1],[5] as well as
the reference lists of all relevant articles were included. We also obtained data outside of the search strategy using expert knowledge of active studies as with the Asia-Pacific Crohn’s and Colitis Epidemiologic Study Group [ACCESS]).

All stages of the systematic review were independently conducted by two teams; the first from the United Kingdom (TT and JSC) and the second from Hong Kong (SCN, VSWL and CYL). The first stage consisted of an initial screening of abstracts and titles of search results. Studies were excluded if they were not observational in design and did not report original data (i.e. review articles). Studies were considered for final inclusion in the review if their study participants consisted of a population-based inception cohort of CD and/or UC with raw numbers reported to enable the calculation of ever and/or never smoking proportion at time of IBD diagnosis. Studies could also be included if they expressed the frequency of smokers or non-smokers. A study was considered to be population-based if the sample was representative of geographical region. Smoking data had to be reported separately in CD and UC cohorts for inclusion. Studies that did not report smoking data from time of diagnosis or did not have the year of IBD diagnosis were excluded. Discrepancies between the reviewers were resolved in conjunction with GGK, SG and SCN. The flow chart for the above process is presented in Fig 1.

**Data analysis**

The data extracted included: author, geographical location, study period, size of CD or UC cohort, frequency of current, former and never-smokers including unknown smoking status. Study quality was ascertained using a modified version of the Newcastle-Ottawa Scale (S2 Table). The modified scale addressed aspects of quality relevant to population-based inception cohorts as well as ascertainment of smoking exposure.

We classified geographic regions according to proximity and economic similarity based upon the United Nations classification of economic region as in our previous work.[1],[5] The regions included are: North America, South America, Eastern Europe, Northern Europe, Southern Europe, Western Europe, Asia and Oceania.

Scatter plots (created using Plotly (Montreal, Canada) were used to display time trends across geography in the proportion of never and ever smokers in inception cohorts of CD (Fig 2) and UC (Fig 3) between 1980 to 2013. The earliest and latest years for which smoking data was available was 1980 and 2013 respectively. Smoking prevalence in local jurisdictions/regions were extrapolated to the entire country. In studies that reported smoking prevalence across a range of years, the median year was selected. Where studies reported former smokers, these patients were pooled with current smokers to formulate an ever-smoker category. In studies that reported only current and former category or an ever smoker category, the remainder of the population were designated as never-smokers. In UC, we sought to assess the former smoker population as this is considered the at-risk population. However, the former smoker population was also incorporated into the ever smoker population and reported for consistency. Studies with a total sample size of less than 10 subjects were excluded from these graphs. Further analysis in the form of meta-analysis or time trend analyses were not deemed appropriate due to paucity of data and heterogeneity in study design. Apart from ever smoking and never smoking data, quantitation of smoking in terms of average number of cigarettes smoked or duration of smoking were not available from the population based epidemiological data.

**Results**

We identified 41 records from our previous research on IBD inception cohorts[4]. Our search strategy identified 3152 additional records from MEDLINE and Embase from January 1948 to April 31st 2018. Fig 1 demonstrates the number of records eligible for and removed prior to
41 studies from published systematic reviews

3154 citations identified from literature search
1478 from Medline
1676 from Embase

3195 citations eligible for screening

3034 citations excluded in screening of titles and abstracts with general criteria

161 articles eligible for full-text review

105 articles excluded after full-text review for the following reasons:
- Year of diagnosis of IBD missing
- No data on smoking prevalence
- No confirmation that smoking data was from time of IBD diagnosis
- Duplicates

56 studies eligible for inclusion in the systematic review

Fig 1. Study selection.

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full text review. 56 studies were eligible for final inclusion in the systematic review. These included 44 studies in CD and 46 studies in UC (Fig 1). Characteristics of all included studies are presented in Tables 1 and 2.

Smoking prevalence figures were reported for: North America (2 studies), South America (1 study), Eastern Europe (3 studies), Northern Europe (16 studies), Southern Europe (12 studies), Western Europe (4 studies), Asia (15 studies), and Oceania (3 studies). Scatter plots representing never-smoker prevalence in the CD and UC cohorts from 1980 to 2018 stratified by geographic region are presented in Figs 2 and 3 respectively. Smoking prevalence varied greatly according to geographic region. Fig 2 shows that an increasing number of the newly diagnosed CD population over the last two decades in the West particularly in the UK have never smoked. In contrast, a decrease in the proportion of never-smokers over the 1990s and 2000s is seen in newly industrialised nations such as China. Fig 3 is suggestive of significant heterogeneity in the trend of the never-smoker group in the newly diagnosed UC population in the West. Data from the United Kingdom and Sweden over the 1980s and 1990s suggest a decrease in this group whilst data from Iceland and Italy show an increase in the never-smoking proportion. Fig 3
Fig 2. The proportion of never smokers at diagnosis in global population-based inception cohorts of Crohn’s disease stratified by region, country and year (1946–2018).

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Fig 3. The proportion of never smokers at diagnosis in global population-based inception cohorts of ulcerative colitis stratified by region, country and year (1946–2018).

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| Author | Country | Area | Year | Total CD (n) | Age Category | Age: Mean (SD, Median, Range) | Ever Smoker (n) | Ever Smoker (%) | Never Smoker (n) | Never Smoker (%) | Missing Data | Defined smoking groups* |
|--------|---------|------|------|-------------|--------------|-------------------------------|----------------|----------------|----------------|----------------|-------------|--------------------------|
| Leong 2004 | China | Hong Kong | 1985–2001 | 80 | all ages | 33.1 (14)* | 20 | 25 | 60 | 75 | 0 | Yes |
| Lok 2007 | China | Hong Kong | 1991–2006 | 27 | all ages | 26 (11–56)* | 2 | 7.4 | 25 | 92.6 | 0 | Yes |
| Zhao 2013 | China | Wuhan | 2010 | 34 | all ages | 36* | 22 | 65 | 12 | 35 | 0 | Yes |
| Zeng 2013 | China | Guangdong | 2011–2012 | 17 | all ages | 25* | 2 | 11.8 | 15 | 88.2 | 0 | Yes |
| ACCESS Study | China | Nationwide | 2011–2013 | 142 | - | - | 38 | 26.8 | 104 | 73.2 | 3.4 | Yes |
| Yang 2014 | China | Daqing | 2012–2013 | 2 | all ages | 39.5* | 100 | 0 | 0 | 0 | Yes |
| Zahedi 2014 | Iran | Kerman | 2011–2012 | 6 | all ages | 33.3* | 33.3 | 4 | 66.6 | 0 | No |
| Tozun 2009 | Turkey | Nationwide | 2001–2003 | 216 | all ages | 37.4 (12.8)* | 87 | 40.3 | 129 | 59.7 | 0 | Yes |
| Lakatos 2013 | Hungary | Veszprem | 1977–2001 | 506 | all ages | 31.5 (13.8)* | 239 | 55.7 | 224 | 44.3 | 0 | No |
| Lakatos 2011 | Hungary | Veszprem | 2002–2006 | 163 | all ages | 32.5 (15.1)* | 81 | 49.8 | 82 | 50.2 | 0 | Yes |
| Garcia 2005 | UK | Bradford | 1995–1997 | 171 | 20–84 | 79 | 46.2 | 74 | 43.3 | 10.5 | Yes |
| Tsironi 2004 | UK | Tower Hamlets | 1997–2001 | 19 | all ages | 19 (10–75)* | 6 | 31.6 | 13 | 68.4 | 0 | No |
| Ramadas 2010 | UK | Cardiff | 1986–1991 | 105 | all ages | 30 (4–78)* | 52 | 49 | n/a | n/a | 0 | No |
| Yapp 2000 | UK | Cardiff | 1991–1995 | 84 | all ages | - | 36 | 43 | 32 | 38 | 19 | Yes |
| Ramadas 2010 | UK | Cardiff | 1992–1997 | 99 | all ages | 29 (12–73)* | 39 | 39 | n/a | n/a | 0 | No |
| Garcia 2005 | UK | Nationwide | 1995–1997 | 171 | 20–84 | - | 79 | 46.2 | 74 | 43.3 | 10.5 | Yes |
| Persson 1990 | Sweden | Stockholm County | 1984–1987 | 152 | >15 years | - | 101 | 66.5 | 48 | 31.6 | 1.97 | Yes |
| Sjoberg 2014 | Sweden | Uppsala | 2005–2009 | 264 | all ages | 34.8 (19.4)* | 81 | 30.7 | 113 | 42.8 | 26.5 | Yes |
| Kiudelis 2012 | Lithuania | Kaunas | 2007–2009 | 16 | all ages | 34.94 (10.4)* | 6 | 37.5 | 10 | 62.5 | 0 | Yes |
| Bjornsson 1998 | Iceland | Nationwide | 1980–1989 | 75 | all ages | 34.4 (4–79)* | 18 | 24 | 7 | 9.3 | 66.7 | Yes |
| Bjornsson 2000 | Iceland | Nationwide | 1990–1994 | 64 | all ages | 29.7 (9–76)* | 20 | 31.3 | 27 | 42.1 | 26.6 | Yes |
| Bjornsson 2015 | Iceland | Nationwide | 1995–2009 | 279 | all ages | 38 (3–86)* | 76 | 27.2 | n/a | n/a | 35 | No |
| Hammer 2016 | Faroe Islands | Faroe Islands | 1960–2014 | 113 | all ages | 41* | 52 | 54 | 43 | 46 | 0 | Yes |
| Vind 2006 | Denmark | Copenhagen | 2003–2005 | 209 | all ages | 31 (10–85)* | 108 | 51.7 | 92 | 44 | 4.3 | Yes |
| Vucelic 1991 | Croatia | Zagreb | 1975–1989 | 106 | all ages | - | 52 | 49 | n/a | n/a | n/a | No |
| Manousos 1996 | Greece | Heraklion | 1990–1994 | 37 | all ages | - | 28 | 76 | 9 | 24 | 0 | Yes |
| Franceschi 1987 | Italy | Milan | 1983–1984 | 109 | all ages | - | 82 | 75.23 | 17 | 15.6 | 0 | Yes |
| Tragnone 1993 | Italy | Bologna | 1986–1989 | 38 | >10 years | 36.6 (10–80)* | 18 | 48 | 20 | 52 | 0 | Yes |
| Ranzi 1996 | Italy | Crema and Cremona | 1990–1994 | 40 | all ages | - | 15 | 39 | 23 | 61 | 5 | Yes |
| Cottone 2006 | Italy | Casteltermini | 1979–2002 | 29 | all ages | 29 (17–62)* | 20 | 68.9 | 9 | 31 | 0 | Yes |
| Fraga 1997 | Spain | Barcelona | 1997 | 54 | - | 37 (14)* | 30 | 55.5 | 24 | 44 | 0 | Yes |
| Rodrigo 2004 | Spain | Oviedo | 2000–2002 | 37 | all ages | 33 (15)* | 17 | 46 | n/a | n/a | 0 | No |

(Continued)
shows that the proportion of people who have never smoked at UC diagnosis in newly industrialised nations particularly China has been decreasing over the last two decades. Tables 3 and 4 displays these ranges stratified according to geographic region.

Table 1. (Continued)

| Author                | Country  | Area            | Year       | Total CD (n) | Age Category | Age; Mean (SD), Median (Range) | Ever Smoker (n) | Ever Smoker (%) | Never Smoker (n) | Never Smoker (%) | Missing Data | Defined smoking groups* |
|-----------------------|----------|-----------------|------------|--------------|--------------|-------------------------------|----------------|-----------------|------------------|-------------------|--------------|-------------------------|
| Garrido 2004[26]      | Spain    | Huelva          | 1980–2003  | 30           | all ages     | 32.3 (13–42)*                 | 10             | 66.7            | n/a              | n/a               | n/a          | No                      |
| **Western Europe (n = 4)** |          |                 |            |              |              |                               |                |                 |                  |                  |              |                         |
| Abakar-Mahamat 2007[22] | France   | Corsica         | 2002–2003  | 20           | all ages     | 29 (11–58)*                   | 7              | 35              | 13               | 65                | 0            | No                      |
| Ott 2008[23]          | Germany  | Oberpfalz       | 2004–2006  | 168          | all ages     | 28.9 (1–75)*                  | 62             | 36.9            | 106              | 63.1              | 0            | Yes                     |
| Van der Heide 2011[20] | Netherlands | Leeuwarden    | 1996       | 128          | ≥18 years    | 30 (23–42)*                   | 90             | 70.3            | 38               | 29.7              | 0            | Yes                     |
| Romberg-Camps 2008[21] | Netherlands | South Limburg | 1991–2002  | 476          | all ages     | 34 (5–79)*                    | 328            | 69              | 148              | 31                | 0            | Yes                     |
| **Oceania (n = 2)** |          |                 |            |              |              |                               |                |                 |                  |                  |              |                         |
| Vegh 2014[44]         | Australia | Melbourne       | 2011       | 38           | ≥15 years    | 37 (17–77)*                   | 13             | 34.2            | 20               | 52.6              | 13.2         | Yes                     |
| Niewiadomski 2015[72] | Australia | Victoria        | 2007–2013  | 146          | all ages     | 36 (11–82)*                   | 32             | 22              | 114              | 78                | 0            | No                      |
| **North America (n = 1)** |          |                 |            |              |              |                               |                |                 |                  |                  |              |                         |
| Edwards 2008[73]      | Barbados  | Nationwide      | 1980–2004  | 47           | all ages     | -                             | 2              | 4               | n/a              | n/a               | n/a          | No                      |
| **South America (n = 1)** |          |                 |            |              |              |                               |                |                 |                  |                  |              |                         |
| Parente 2015[74]      | Brazil    | Piaui           | 2011–2012  | 100          | ≥18 years    | 32.9 (13.6)*                  | 21             | 21              | 79               | 79                | 0            | No                      |

*The study defined the current smoker and former smoker or never smoker groups. Alternatively, the authors quantified missing data.

shows that the proportion of people who have never smoked at UC diagnosis in newly industrialised nations particularly China has been decreasing over the last two decades. Tables 3 and 4 displays these ranges stratified according to geographic region.

**Crohn’s disease**

Smoking prevalence data at diagnosis of CD was collected from twenty countries. The western world particularly Europe has demonstrated an overall increase in the prevalence of never smokers in the newly diagnosed CD cohort over the last three decades.

In Sweden (Northern Europe), the proportion of never-smokers increased from 31.6%[16] in the 1980s to 42.8% (2007)[17]. In the early 1990s, the proportion of never-smokers in the newly diagnosed CD cohort in the UK was 38%.[18] A large population-based inception cohort study (1989–2009)[19] in the UK estimated that 64.6% of newly diagnosed CD patients were never-smokers. This trend is replicated in Western Europe, Southern Europe and Eastern Europe. The proportion of never-smokers in the CD cohort in the Netherlands ranged from 29.7%[20] to 31%[21] in the 1990s however France and Germany demonstrated a never-smoker proportion of 65%[22] and 63.1%[23] in the 2000s respectively. In Italy (Southern Europe), there was a steady increase in the never-smoker population at CD diagnosis over the course of the 1980s[24] and 1990s.[25] Similarly, Spain showed consistent trends with the ever-smoker group steadily declining from 66%(1980 and 1990s)[26] to 46%(2001)[27] in the newly-diagnosed CD cohort. Similarly, in Hungary (Eastern Europe), the proportion of never smokers in the newly diagnosed CD cohort increased from 44.3%[8] to 50.2%[28] over the course of 30 years.
Table 2. Smoking prevalence in global population-based inception cohorts of ulcerative colitis stratified by region, country and year (1946–2018).

| Author            | Year                  | Total UC (n) | Age Range | Age Mean (SD), Median (Range) | Ever Smoker (n) | Ever Smoker (%) | Former-Smoker (n) | Former-Smoker (%) | Never Smoker (n) | Never Smoker (%) | Missing Data (%) |
|-------------------|-----------------------|--------------|------------|-------------------------------|----------------|----------------|------------------|------------------|----------------|-----------------|-----------------|
| Chow 2009[41]     | Hong Kong 1985–2006   | 37 (12–85)   | 15.1       | n/a                           | n/a            | n/a            | 146              | 84.9             | 0              | Yes             | 15              |
| Lai 2006[42]      | China Hong Kong 1990–2006 | 38 (14–72)   | 26          | 15.1                           | n/a            | n/a            | 146              | 84.9             | 0              | Yes             | 15              |
| Zhou 2017[43]     | China Hong Kong 2003–2012 | 38 (12–85)   | 26          | 15.1                           | n/a            | n/a            | 146              | 84.9             | 0              | Yes             | 15              |
| ACCESS Study 2012 | China Nationwide 2015–2013 | 38 (12–85)   | 26          | 15.1                           | n/a            | n/a            | 146              | 84.9             | 0              | Yes             | 15              |
| ACCESS Study 2013 | China Nationwide 2015–2013 | 38 (12–85)   | 26          | 15.1                           | n/a            | n/a            | 146              | 84.9             | 0              | Yes             | 15              |
| Nakamura 2009     | Japan 1988–1990        | 38 (12–85)   | 26          | 15.1                           | n/a            | n/a            | 146              | 84.9             | 0              | Yes             | 15              |
| Gheorghie 2004    | Turkey Nationwide 2001–2003 | 38 (12–85)   | 26          | 15.1                           | n/a            | n/a            | 146              | 84.9             | 0              | Yes             | 15              |
| Eastern Europe (n = 11) | Northern Europe (n = 11) | 38 (12–85)   | 26          | 15.1                           | n/a            | n/a            | 146              | 84.9             | 0              | Yes             | 15              |

(Continued)
| Author                | Year          | Area            | Total UC (n) | Age Range | Age Mean (SD, Median* (Range)) | Ever Smoker (%) | Former Smoker (n) | Never Smoker (n) | Never Smoker (%) | Missing Data (%) | Defined smoking groups* |
|----------------------|---------------|-----------------|--------------|-----------|-------------------------------|-----------------|------------------|------------------|------------------|------------------|---------------------|
| Garcia 2005[32]      | UK Nationwide| 1995–1997       | 222          | -         | 28 (11–73)*                   | 10              | 62.5             | 3                | 18.8             | 6                | 37.5                | No                  |
| Tsironi 2004[33]     | UK Tower Hamlets| 1997–2001     | 16           | all ages  | 20–84                         | 21              | 36.5             | 2               | 12.2             | 130              | 58.6                | 12.6                | Yes                |
| Vucelic 1991[80]     | Croatia       | Zagreb          | 265          | all ages  | 1975–1989                      | 81              | 30.5             | 51               | 19.2             | 184              | 69.5                | 0                   | No                  |
| Ladas 2005[81]       | Greece        | Trikala         | 66           | ≥10 years | 1990–1994                      | 29              | 44               | 16               | 24.3             | 37               | 56                  | 0                   | Yes                |
| Manousos 1996a[82]   | Greece        | Heraklion       | 117          | all ages  | 1990–1994                      | 74              | 63.3             | 60               | 51.3             | 43               | 36.7                | 0                   | No                  |
| Franceschi 1987[24]  | Italy         | Milan           | 124          | all ages  | 1983–1984                      | 72              | 58.1             | 46               | 37.1             | 52               | 41.9                | 0                   | Yes                |
| Tranzone 1993[40]    | Italy          | Bologna         | 73           | ≥10 years | 1986–1989                      | 44.2 (16–74)*   | 49               | 68               | 31               | 43               | 24                  | 33                  | Yes                |
| Ranzi 1996[25]       | Italy          | Crema and Cremona| 82       | all ages  | 1990–1994                      | 45              | 56               | 32               | 39               | 35               | 44                  | 2.4                 | Yes                |
| Garrido 2004[26]     | Spain          | Huelva          | 40           | all ages  | 1980–2003                      | 44.7 (39–51)*   | 5                | 12.5             | n/a              | n/a              | n/a                 | n/a                 | No                  |
| Fraga 1997[39]       | Spain          | Barcelona       | 86           | ≥10 years | 1997                           | 40 (15)*         | 41               | 48               | 18               | 21               | 45                  | 52                  | 0                   | Yes                |
| Rodrigo 2004[27]     | Spain          | Oviedo          | 47           | all ages  | 2000–2002                      | 45 (20)*         | 19               | 40               | n/a              | n/a              | n/a                 | n/a                 | No                  |
| Abakar-Mahamat 2007[22]| France       | Corsica         | 49           | all ages  | 2002–2003                      | 44 (18–80)*      | 11               | 22.5             | 8                | 16.3            | 38                  | 77.6                | 0                   | No                  |
| Ott 2008[33]         | Germany        | Oberpfalz       | 105          | all ages  | 2004–2006                      | 39.5 (7–81)*     | 44               | 41.9             | 32               | 30.5            | 61                  | 58.1                | 0                   | Yes                |
| Van der Heide 2011[20]| Netherlands  | Leeuwarden      | 192          | ≥18 years | 1996                           | 35 (27–50)*      | 107              | 55.8             | 60               | 31.3            | 85                  | 44.3                | 0                   | Yes                |
| Romberg-Camps 2008[21]| Netherlands | South Limburg  | 630          | all ages  | 1991–2002                      | 42 (8–84)*       | 403              | 64               | 277              | 44              | 227                 | 36                  | 0                   | Yes                |
| Abraham 2003[43]     | Australia      | Sydney          | 102          | all ages  | 1990–1993                      | -               | 42               | 41.2             | 30               | 29.4         | 60                  | 58.8                | 0                   | Yes                |
| Vegh 2014[44]        | Australia      | Melbourne       | 27           | ≥15 years | 2011                           | 40 (17–87)*      | 11               | 40.7             | 10               | 37              | 8                   | 29.6                | n/a                 | Yes                |
| Niewiadomski 2015[72]| Australia     | Victoria        | 96           | all ages  | 2007–2013                      | 40 (11–87)*      | 22               | 23               | 17               | 18              | 74                  | 77                  | 0                   | No                  |
| Edwards 2008[73]     | Barbados       | Nationwide      | 121          | all ages  | 1980–2004                      | -               | 3                | 2                | n/a              | n/a             | n/a                 | n/a                 | No                  |
| Yamamoto-Furusho 2009[83]| Mexico      | Mexico City     | 848          | all ages  | 1987–2006                      | 31.3 (12.3)*     | 73               | 8.6              | 73               | 8.6             | 775                 | 91.3                | 0                   | Yes                |
| Parente 2015[74]     | Brazil         | Piaui           | 152          | ≥18 years | 2011–2012                      | 36.8 (14.8)*     | 32               | 21.1             | n/a              | n/a             | 120                 | 78.9                | 0                   | No                  |

Table 2. (Continued)

*The study defined the current smoker, former smoker or never smoker groups. Alternatively, the authors quantified missing data.

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In contrast to Europe, smoking prevalence in inception CD cohorts in Asia appears to be increasing over time. The majority of CD subjects in Asia were never-smokers. The proportion of subjects who had never smoked range from 75%[29] (Hong Kong, China;1985–2001) to 92.6%[30] (Hong Kong, China;1991–2006). However, in a more recent inception cohort from Asia from 2011-2013(ACCESS), 73.2% of CD subjects were never smokers. Nine out of 44 studies did not report former smokers. Never-smoker populations were assumed to be the remainder of the population if ever smoker data was provided.

**Ulcerative colitis**

Smoking prevalence data at diagnosis of UC was collected from twenty-five countries. Smoking trends in Europe for the newly diagnosed UC cohort showed more heterogeneity than in CD. Data from the United Kingdom appear to suggest a decrease in the never-smoker proportion in the UC cohort during the 1990s; 66.2%(1993)[31] to 58.6%(1995–1997)[32] and 37.5% (1999)[33]. The former smoker population appears to have decreased in the same decade from 21.6%[31] to 18.8%[33]. Data from Sweden demonstrate reduction in the never smoker population from 52.4%(1984–1987)[16] to 32.5%(2005–2009)[34]. An increase in the proportion of former smokers at diagnosis from 17.9%(1984–1987)[16] to 24.7%(2005–2009)[34] was noted. Other Scandinavian regions such as Denmark showed only a slightly higher proportion of never smokers in their UC cohorts; 45%(2004)[35]. In contrast to the remainder of Northern Europe in the 1980s and 1990s, Iceland demonstrated an increase in the never-smoker proportion from 13.5%[36] to 35.8%[37] across this period. The percentage of former smokers at UC

### Table 3. Prevalence of never-smokers in global population-based inception cohorts of Crohn’s disease and ulcerative colitis stratified by range and region (1946–2018).

| Region          | Crohn’s disease | Ulcerative colitis |
|-----------------|-----------------|--------------------|
|                 | Lowest estimate | Highest estimate  |
|                 | Lowest estimate | Highest estimate  |
| North America   | n/a             | n/a                |
| South America   | n/a             | 79% (n = 100) 2011–2012; Piaui, Brazil |
| Eastern Europe  | 44.3% (n = 506) 1977–2001; Veszprem, Hungary | 65.5% (n = 220) 2002–2006; Veszprem, Hungary |
| Northern Europe | 9.3% (n = 75) 1980–1989; Nationwide, Iceland | 13.5% (n = 282) 1980–1989; Nationwide, Iceland |
| Southern Europe | 15.6% (n = 109) 1983–1984; Milan, Italy | 33% (n = 73) 1986–1989; Bologna, Italy |
| Western Europe  | 29.7% (n = 128) 1996; Leeuwarden, Netherlands | 36% (n = 630) 1991–2002; South Limburg, Netherlands |
| Asia            | 35% (n = 34) 2010; Wuhan, China | 46.9% (n = 49) 1998–2002; Trakya, Turkey |
| Oceania         | 52.6% (n = 38) 2011; Melbourne, Australia | 29.6% (n = 27) 2011; Melbourne, Australia |

N: total cohort size; n/a: not available; Studies with n<10 have been excluded.

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diagnosis also rose from 11.7% to 20% across those two decades. These results correlate with a decrease in the ever-smoker proportion down to 48%[38] in the 21st century.

In Southern Europe, Spain demonstrated an increase in their ever-smoker proportion from 12.5%[26] in the 1980s and 1990s to 48%[39] in the 2000s. In Italy, the never-smoker proportion varied by geographic region; 42% (Milan; early 1980s)[24] to 33% (Bologna; late 1980s)[40] and 44% (Crema and Cremona; early 1990s)[25]. Former-smoker proportions were similarly varied across these regions and time periods: 37.1%, 43% and 39% respectively. In Eastern Europe, Veszprem (Hungary) demonstrated a reduction in the never-smoker population in the UC cohort; 67.5%(1977–2008)[8] to 65.5%(2002–2006)[28]. The former smoker population in the newly diagnosed UC cohort during those periods were 17.6% and 20.9% respectively. In contrast to the rest of Europe, never-smoker proportions increased over the late 1990s and early 2000s in Western Europe from 44.3%(2002–2006; Leeuwarden, Netherlands) to 77.55%(France; 2003)[22] and 58.09%(Germany;2005)[23].

The proportion of newly diagnosed UC subjects who have never smoked has decreased in China over the last two decades. The proportion who had never smoked were 84.9%[41] in China in the late 1990s. By 2012 these figures had decreased to 69.5% (ACCESS Cohort;2011–2013). The proportion of former smoker patients in the newly diagnosed UC cohort in China appears to be increasing from 11%(1990–2006)[42] to 34% (Hong Kong ACCESS cohort).

Data from major cities in Australia suggest that the proportion of never-smokers in the newly diagnosed UC cohort has increased from 58.8%(Sydney;1992)[43] to 77%(Victoria;2007–2013)[44]. The former smoker proportion of patients at diagnosis also decreased from

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**Table 4. Prevalence of ever-smokers in global population-based inception cohorts of Crohn’s disease and ulcerative colitis stratified by range and region (1946–2018).**

| Region            | Lowest estimate | Highest estimate | Ulcerative colitis |
|-------------------|-----------------|------------------|--------------------|
|                   |                 |                  |                    |
| **Crohn’s disease** |                 |                  |                    |
| North America     | n/a             | 4% (n = 47) 1980–2004; Barbados, Nationwide | n/a | 8.6% (n = 848) 1987–2006; Mexico City, Mexico |
| South America     | n/a             | 21% (n = 100) 2011–2012; Piaui, Brazil | n/a | 21.1% (n = 152) 2011–2012; Piaui, Brazil |
| Eastern Europe    | 29.8% (n = 85) 2002–2003; Nationwide, Romania | 55.7% (n = 506) 1977–2001; Veszprem, Hungary | 13.3% (n = 163) 2002–2003; Nationwide, Romania | 34.5% (n = 220) 2002–2006; Veszprem, Hungary |
| Northern Europe   | 24% (n = 75) 1980–1989; Nationwide, Iceland | 66.5% (n = 152) 1984–1987; Stockholm County, Sweden | 5.4% (n = 884) 1995–2009; Nationwide, Iceland | 62.5% (n = 16) 1997–2001; Tower Hamlets, United Kingdom |
| Southern Europe   | 39% (n = 40) 1990–1994; Crema and Cremona, Italy | 76% (n = 37) 1990–1994; Heraklion, Greece | 12.5% (n = 40) 1980–2003; Huelva, Spain | 68% (n = 73) 1986–1989; Barcelona, Spain |
| Western Europe    | 35% (n = 20) 2002–2003; Corsica, France | 70.3% (n = 128) 1996; Leeuwarden, Netherlands | 22.5% (n = 49) 2002–2003; Corsica, France | 64% (n = 630) 1991–2002; South Limburg, Netherlands |
| Asia              | 7.4% (n = 27) 1991–2006; Hong Kong, China | 65% (n = 34) 2010; Wuhan, Turkey | 8.70% (n = 23) 2012; Hyderabad, India | 53% (n = 49) 1998–2002; Trakya, Turkey |
| Oceania           | 22% (n = 146) 2007–2013; Victoria, Australia | 34.2% (n = 38) 2011; Melbourne, Australia | 23% (n = 96) 2007–2013; Victoria, Australia | 41.2% (n = 102) 1990–1993; (Sydney, Australia) |

N: total cohort size; n/a: not available; Studies with n<10 have been excluded.

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29.4% to 18% across the same regions and time periods respectively. The impact of missing smoking data regarding the participants vary due to heterogeneity in reporting. Four out of the 46 studies included for UC did not report former smokers at diagnosis. Never-smoker populations were assumed to be the remainder of the population if ever smoker data was provided.

Discussion

We present a comprehensive review of smoking trends over time in inception IBD cohorts worldwide. In the West, the proportion of newly diagnosed CD subjects who have never smoked has increased over time. The proportion of newly diagnosed UC subjects who have never smoked has declined in the 1980s and 1990s in Europe although an increase was noted in Western Europe from the late 1990s. In contrast, the proportion of subjects who have never smoked at IBD diagnosis has decreased in Asia, particularly in China. Thus, we demonstrate that trends in smoking prevalence specific to the IBD cohort do not mirror global trends in smoking discerned from the general population.[45]

The incidence of IBD in newly industrialised countries is accelerating whilst the incidence of IBD is stabilising in the West.[1] The effect of smoking on the incidence of IBD across the globe likely varies due to heterogeneity in genetic susceptibility and the presence of other risk factors. Public health measures in the 1980s and 1990s led to a reduction of smoking prevalence in the general population in many Western countries.[46] The higher proportion of never smokers at diagnosis of CD over time may be explained by adolescents who decided not to smoke in the 1990s. This could have potentially contributed to the stabilization, and in certain regions decrease, in the incidence of adult-onset CD in some Western countries. This ecological trend could also explain the decrease in the former smoker population in the UK over the 1990s and could have contributed to the recent stabilisation of UC incidence.[1]

In contrast, we are at the infancy of the IBD ‘epidemic’ in newly industrialized countries in Asia, especially in areas of high smoking prevalence[46]; hence ever-smoker trends at IBD diagnosis are on the increase. The rapid expansion of the former smoker population at UC diagnosis in China is suggestive of a rapid expansion of the at-risk population. The Global Burden of Disease Study 2015 identified China as one of the leading countries in the world for the total number of smokers.[46] In line with the Lopez model[47], these newly industrialised nations are rapidly moving towards Stage IV where smoking prevalence in the general population will decrease as societal attitudes shift and government anti-smoking policy becomes comprehensive. This could potentially foreshadow a protracted course of high UC incidence in comparison to CD. Similar to the West, we hypothesise that a ‘lag effect’ can be expected in future epidemiological studies particularly in CD based in newly industrialised nations. However, due to the complex interplay between genetics and environment in the development of IBD, this effect may not be as pronounced as in the West[12] although in contrast to CD, there is some evidence to suggest that the role of smoking in UC is uniform across the East and West.[12,48,49]

The concurrent decrease of the never-smoker population in both CD and UC cohorts in newly industrialised nations is potentially suggestive of significant heterogeneity in the interaction between smoking and the process of IBD development across geographic regions. Even in the West, the incidence of CD had been high in relatively low smoking prevalence populations i.e. Israeli Jews[50], Canada, and Sweden. Multiple studies[12],[29],[51] in the Asia-Pacific region have demonstrated that active smoking does not confer an increased risk of CD in this population as it does in the West. The relative absence of the NOD-2 mutation in CD cases in Japan suggests that the role of smoking in IBD is subject to underlying genetic heterogeneity. [52] Environmental factors such as air pollution[53], diet and a Western lifestyle as demonstrated in migrant sub-populations[6] as well as evolving early life feeding patterns and
improved hygiene as part of socioeconomic development\cite{12} could be more potent mediators of IBD development\cite{54,55}.

Our study has several limitations predominantly due to lack of available data. We were unable to perform a meta-analysis or ecological trend analysis due to study heterogeneity. Small sample sizes in some studies have also increased the risk of imprecise estimates for smoking prevalence. A paucity of gender-specific, age-category specific smoking prevalence data, data relating to quantification of smoking habits or breakdown of rural vs. urban data in the IBD cohort did not allow for further sub-group analysis. Although, it is possible studies that included children and adolescents would have a higher prevalence of never-smokers, summary statistics from included studies suggest this is not the case. The exposure to smoking was reported inconsistently; some studies reported current and former smokers whilst others reported ever and never smokers. Twenty three out of ninety-five included cohorts reported missing smoking data on participants (Tables 1 and 2). No data was available regarding second-hand smoking exposure. Due to differing study periods and the generalisation of regions to represent countries, smoking data was not fully homogenous. The inequalities in healthcare access across the globe can also affect data collection and reporting. In addition, we acknowledge that the attributable risk of smoking on IBD is low (i.e. most IBD patients do not have a history of smoking [current or former] prior to their diagnosis), however it remains an important risk mediator in the development of IBD.

Despite these limitations, this study provides a comprehensive overview of the prevalence of smoking in the global IBD cohort across time and geography. The proportion of never-smokers in IBD cohorts from newly industrialised countries appears to be decreasing over time in contrast to the IBD cohorts in the West. In light of our previous work and this study, it appears that IBD epidemiological patterns globally can be modelled along geographical and development lines within a context of genetic heterogeneity and environmental ecological exposures. It remains of clinical importance for medical practitioners to record information and act on smoking status for patients with IBD regardless of geography and ethnicity, especially in light of data suggesting smoking confers an adverse disease course in CD and is a risk factor in non-response to anti-TNF therapy\cite{14}. Large-scale prospective inception cohorts assessing the associations of smoking for both UC and CD in Eastern and Western populations will add to the available data.

This is the first systematic review to assess trends in the prevalence of smoking in the IBD cohort worldwide. It provides a foundation for future work assessing the prevalence of this important risk mediator in a global setting as well as highlighting some of the challenges surrounding this data. A deeper understanding of IBD aetiology in relation to diet and other environmental factors across geographic regions and ethnicities is urgently required in order to formulate strategies to slow the global increase in the incidence of IBD.

Supporting information

S1 Table. Detailed MEDLINE and EMBASE search strategy for article selection (1 January 1947 to April 5 2018).

(DOCX)

S2 Table. Quality assessment of manuscripts (modified Newcastle Ottawa scale).

(DOCX)

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