Incidence of Crohn's disease in children and adolescents correlates with socioeconomic and environmental factors: a systematic review and meta-regression

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Abstract

Background: The worldwide incidence of Crohn's disease (CD) in childhood and adolescence has an increasing trend, with significant differences between different geographic regions and individual countries. This includes an increase in the incidence of CD in countries and geographic regions where CD was not previously prevalent. In response to the increasing incidence, the pediatric care landscape is facing growing challenges.

Objective: This systematic review and meta-analysis were undertaken to comprehensively delineate the incidence rates of Crohn's disease in pediatric populations across different countries and to explore potential influencing factors.

Methods: We performed a systematic review of PubMed and EMBASE (via OVID) for studies from 01/01/1970 to 12/31/2019. In addition, a manual search was performed in relevant and previously published reviews. The results were evaluated quantitatively. For this purpose, random effects meta-analyses and meta-regressions were performed to investigate the overall incidence rate and possible factors influencing the incidence.

Results: A qualitative synthesis of 74 studies was performed, with 72 studies included in the meta-analyses and 52 in the meta-regressions. The results of our meta-analysis showed significant heterogeneity between the individual studies, which cannot be explained by a sample effect alone. Our findings showed geographical differences in incidence rates, which increased with increasing distance from the equator, although no global temporal trend was apparent. The meta-regression analysis also identified geographic location, UV index, and human development index as significant moderators associated with CD incidence.

Conclusions: Our results suggest that pediatric CD incidence has increased in many countries since 1970, but varies widely with geographic location, which may pose challenges to respective health care systems. We identified geographic, environmental, and socioeconomic factors that contribute to the observed heterogeneity in incidence rates. These results can serve as a basis for future research. To this end, implementations of internationally standardized and interoperable registries combined with the dissemination of health data through federated networks based on a Common Data Mode (CDM), such as the Observational Medical Outcomes Partnership (OMOP CDM), would be beneficial. This would deepen the understanding of CD and promote evidence-based approaches to preventive and interventional strategies as well as inform public health policies aimed at addressing the increasing burden of CD in children and adolescents.

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Systematic Review and Meta-Regression

Incidence of Crohn's disease in children and adolescents correlates with socioeconomic and environmental factors: a systematic review and meta-regression

Jens Weidner [1]*, Ingmar Glauche[1], Ulf Manuwald [2,3], Ivana Kern[2], Ines Reinecke[1], Franziska Bathelt[1,4], Makan Amin [2,5], Fan Dong[2], Ulrike Rothe[6] and Joachim Kugler [2]

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Abstract:

Background: The worldwide incidence of Crohn's disease (CD) in childhood and adolescence has an increasing trend, with significant differences between different geographic regions and individual countries. This includes an increase in the incidence of CD in countries and geographic regions where CD was not previously prevalent. In response to the increasing incidence, the pediatric care landscape is facing growing challenges. This systematic review and meta-analysis were undertaken to comprehensively delineate the incidence rates of Crohn's disease in

pediatric populations across different countries and to explore potential influencing factors.

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Keywords: Crohn´s disease; inflammatory bowel disease; pediatric,

Introduction

Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis (IBD-U) are chronic inflammations of the gastrointestinal tract and are summarized under inflammatory bowel disease (IBD). Since the beginning of the 21st century, a progression in incidence, mainly due to CD, has been observed in both industrialized and emerging countries [1,2] IBD are immune-mediated diseases that can affect people of all ages. However, about 20 % of IBD cases are diagnosed before the age of 20, with an adverse shift in the age of diagnosis to early childhood years. Approximately 25% of children and adolescents are younger than 10 years of age at diagnosis and 4% are younger than 5 years of age [2–5]. International epidemiologic data on CD vary considerably concerning the country and calendar year, and temporal trends are also controversial [1,6]. With an annual incidence of IBD of 5 to 11 per 100,000 children and adolescents, pediatrics faces growing problems [3,5,7]. The incidence of CD is significantly higher compared to CU [1,8], therefore the following will focus on CD.

The etiology of CD is still not definitively understood. However, the etiology seems to be multifactorial and consists of an interaction of genetic, environmental, and lifestyle factor [9–11]. For IBD, the Western lifestyle has been discussed as the cause of CD for some time [12,13]. A similar international progression of incidence has also been observed for other immune-mediated chronic diseases, and inferences have been made about the influence of the Western lifestyle as measured by socioeconomic factors. For example, in their meta-analysis of diabetic ketoacidosis in type 1 diabetes, Große et al. (2018) identified an association between incidence and geographic as well as socioeconomic factors [14]. Several studies also reported variations between incidence and geographic latitude for IBD [10,15]. The increase of CD incidence with latitude supports the

hypothesis that higher residential sun exposure is associated with a lower risk of IBD. The results of these studies have been interpreted to suggest that low vitamin D status may be a risk factor for IBD [16]. The prevalence of vitamin D deficiency is global. Available data suggest that it occurs regardless of the development of the respective countries or the geographic latitude. Accordingly, consistent evidence indicates that the prevalence of vitamin D deficiency is highest in Asia, the Middle East, Africa, and countries with higher latitudes [17,18]. The medical and health-economic relevance of treating children and adolescents with IBD continues and is based on observations in several international studies, with the result that the number of pediatric IBD has increased and the onset of the disease seems to be shifting to early childhood. The impact of this shift in new cases is associated with a high individual as well as the societal burden of disease and will place a heavy burden on the respective healthcare systems [5,13,19,20]. The aim of the current study is to describe global trends in the incidence of CD since 1970 and to identify possible factors influencing the increasing incidence.

Methods

A systematic review was conducted for IBD disorders. Studies were initially included from 1970 - 2019. An ethics vote was not required for the systematic review because patients were not directly involved in the study. The systematic review is registered in Prospero (PROSPERO-NR: CRD42020168644). To improve transparency in methodology, the study protocol for this review was published as "Study protocol epidemiology of inflammatory bowel disease in childhood and adolescence: a systematic review" [21].

The systematic literature search was performed in the PubMed and Embase databases via OVID. In addition, a manual search was performed in bibliographies of previously published and relevant systematic reviews. For detailed methodology and screening of the systematic review we refer to the published study protocol [21https://doi.org/10.1136/bmjopen-2020-037669].

For the current study, we updated the previous systematic review from 2019/2020 in 2022. In this update, which was carried out until August 2022, we used the same search term as before, but also included studies published up to December 31, 2021, which covered the observation period from 1970 to 2019.The inclusion and exclusion criteria shown in Table 1 were defined for this study.

Table 1: Inclusion and exclusion criteria for the present systematic review and meta-analysis according to the PICOS scheme

	Inclusion Criteria	Exclusion criteria
Population	children and adolescents aged 0-18 years	> 18 years of age
Intervention	Incidence	no incidence
Comparsion	Geographical characteristics, environmental factors, economic factors	-
Outcome	CD	no IBD, UC, IBD-U studies with unreported diagnostic criteria
Type of Study	cohort studies and register studies respectively, prevalence studies and cross-sectional studies respectively (population based)	case-control studies, systematic reviews, meta-analyses, case studies
Language	English, French, German	all others

The title-abstract-screening and the full-text-screening were carried out independently by two project participants. The extraction of the data and the corresponding consistency checks were also carried out by two project participants. In case of disagreement, a third project participant was consulted for mediation. All included studies were evaluated for study quality. The critical appraisal tools CASP and SIGN were used for this purpose. In addition, a risk of bias analysis, following the procedure described in the Cochrane Handbook [22], was performed (see Supplement). Studies of poor quality

were not excluded from the quantitative synthesis to avoid loss of information.

Data extraction

All included studies were independently screened for incidence rates and study characteristics using a standardized table summary of findings. In case of missing data, contact with the authors was made. The data were exported to a database and processed for statistical analysis. For studies by one author that reported multiple incidence rates for children and adolescents, the mean values of incidence rates and study sizes were calculated for the respective observation period.

For the planned meta-regression, we classified possible moderators of heterogeneity into two dimensions: geographic and environmental factors on the one hand, and socio-economic factors on the other. Longitude and latitude as well as exposure to ultraviolet sunlight (UVI) were assigned to the 1st dimension of geographical and environmental factors. The geographic data was extracted from Geoplaner V.3.1 [23]. When studies are nationwide or involve multiple centers within a country, the mean latitude value applied to the corresponding country or area was considered. In addition, we used the mean latitude to calculate the absolute distance to the equator irrespective of the northern or southern location [15]. We extracted the UVI from United Nations Sustainable Development Goals (SDGs) data from the WHO database [24].

The 2nd dimension of possible moderators included socioeconomic factors. For this purpose, we used the percentage of gross domestic product (GDP) spent on health, which we extracted from the OECD database "Health expenditure and financing" [25]. The Human Development Index (HDI) was included in the analysis as another possible moderator. The HDI assesses a country's developmental state and combines life expectancy at birth, expected years of schooling, and gross national income per capita [26]. The values relevant to this study were extracted from the United Nations Development Programme's Human Development Reports [26] from 1990 onwards and averaged for statistical analysis. In addition, data on the gross domestic product (GDP) of the respective included countries from the Genesis database of the Federal Statistical Office, were used for a further

moderator analysis [27]. Furthermore, the UHC service coverage index SDG 3.8.1 was extracted from the WHO database [24]. UHC is quantifying coverage of essential health services and is defined as the average coverage based on tracer interventions that include reproductive, maternal, newborn, and child health, infectious diseases, noncommunicable diseases, and service capacity and access among the population [28].

Statistical analysis

We performed random-effects meta-analyses and meta-regressions to assess the variability of incidence rates. Analysis was performed with R version 4.2.1. software using the Metafor package version 3.8-1 [29]. Meta-analysis was performed on a log scale (log incidence rates) using the general inverse variance method. Random effects and the extent of heterogeneity were estimated using the restricted maximum likelihood estimator (REML). For the meta-regression, a multivariate model was constructed to identify further moderators of heterogeneity in incidence rates. The pooled incidence rates for each observation period formed the dependent variable. The observation period for each study was averaged and assigned as the starting time of the given study. The absolute distance of the included countries from the equator, UVI, HDI, health expenditure as a percentage of GDP, GDP, and UHC were included as additional independent variables in the regression model. In addition to the estimate of τ^2, the Q-test for heterogeneity and the I^2 statistic are reported. The I^2-value was interpreted according to Higgins (2002) as follows: 0%-40%, possibly insignificant; 30%-60%, moderate heterogeneity; 50%-90%, substantial heterogeneity; and 75%-100%, considerable heterogeneity [30]. The influence of the moderators was evaluated using the R^2 statistic as a measure of the explained heterogeneity. An a priori significance level of 5% was set for all statistical methods. To control the risk of publication bias, statistical methods such as the Eggers regression test and the rank correlation test were applied to quantitatively assess the risk of publication bias. In addition, we applied the trim-and-fill analysis and the fail-safe N-analysis (Rosenberg method) to consider and

control the potential risk of publication bias.

Results

Data basis and general assessment of studies

A total of 3153 studies were found from the previous systematic search conducted in 2019. The update of the systematic literature search yielded another 83 records. After removing duplicates, 77 studies were screened in the systematic literature search update. Another 5 studies from the update were included in the qualitative and quantitative synthesis. In total, the systematic literature research resulted in 81 findings from 29 countries with the search terms CD, CU, and IBD-U. Crohn's disease was the subject of a total of 74 studies, which were included in the qualitative synthesis of the present work. Two studies had to be excluded retrospectively due to lack of population reference. The meta-analysis included 72 studies from 26 countries and the meta-regression included 52 studies (Fig. 1).

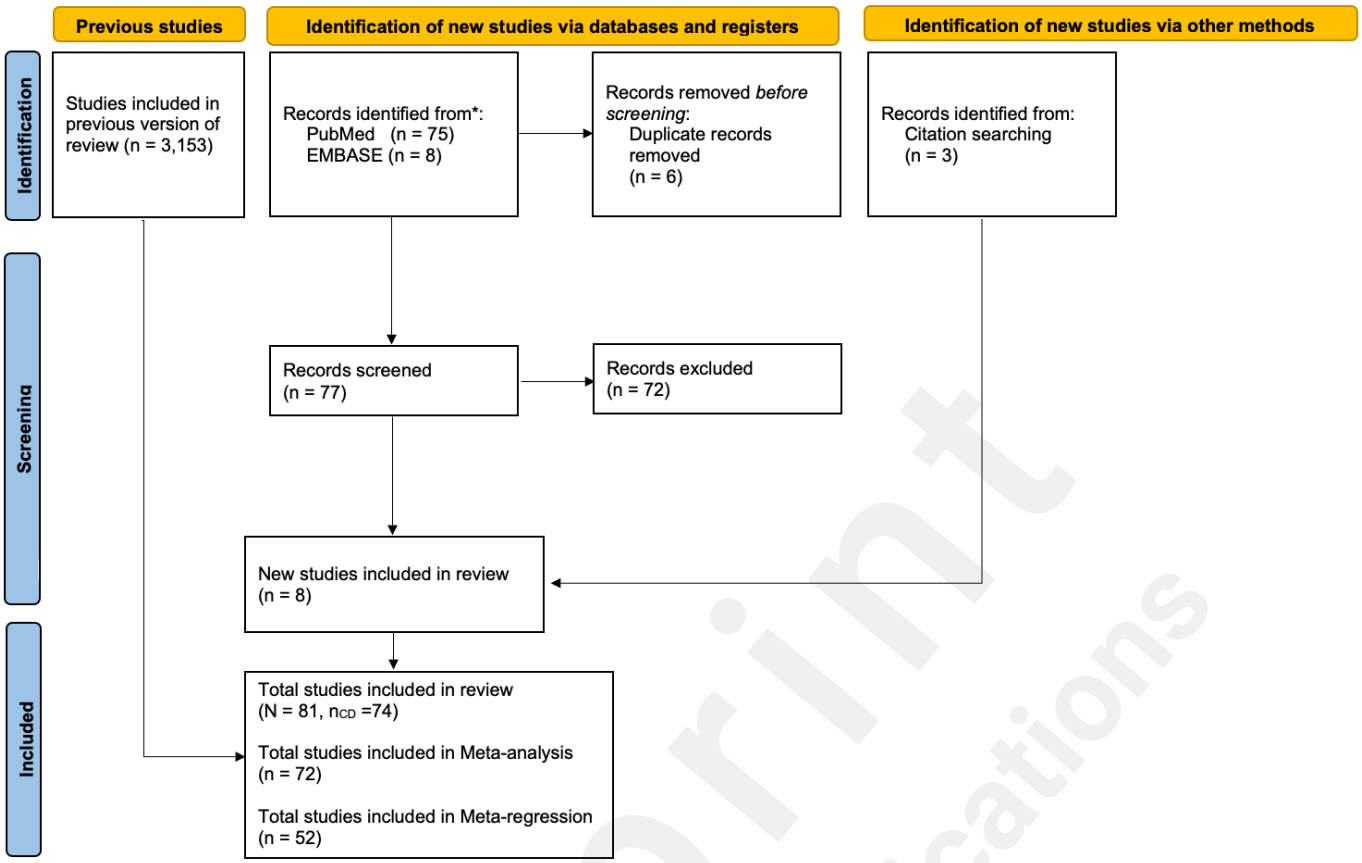

*Figure 1:**PRISMA 2020 flow diagram** for updated systematic reviews which included searches of databases, registers and other sources [31], for our systematic review with meta-analysis and meta-regression*

In the 72 studies eligible for meta-analysis, the incidence rates on the linear scale varied from $0{,}14/10^5$ to $11.40/10^5$. Performing a random-effects meta-analysis revealed that the overall mean incidence rate was $2.64/10^5$ (95% CI: 2.09 – 3.34; on log-Scale -10.54 (95% CI: -10.78 – -10.31), whereas the I^2 value of 97.88% suggests that the substantial heterogeneity of the study results cannot be explained by a sampling effect alone (Fig. S1 in the Supplementary Appendix). In the following we set out to identify factors that can account for the substantial dispersion in study results. Interestingly, the individual weights for each study were largely dominated by the contribution of the between-study variance while the study-specific variance (i.e., the sampling effect) has a smaller effect. Consequently, the studies in the random-effects meta-analysis have rather similar relative weights.

Time as a moderator of CD incidence

We included studies from a 50-year observation period, from 1970 – 2019. In order to assess whether the time point of the study had an influence on the CD incidence, we performed a meta-regression in which *time* is considered the continuous variable, whereas *incidence rates* are the dependent variable. Figure 2 confirms that the moderator *time* has no significant effect on incidence rates for CD. Moreover, *time* as a moderator cannot explain the heterogeneity, so the remaining heterogeneity remains substantial (Test of Moderators P = .39, I^2 = 97.85%, R^2=0.00). These results suggest that there must be other moderators to explain the observed heterogeneity. Figure 2 also displays a slight negative trend with a simultaneous increase in heterogeneity. Some of the studies with low incidence values (depicted in the lower right corner) are from Taiwan, Finland, Saudi Arabia, Mexico and Argentina, reinforcing the impression of greater geographical division. In the next step, we specifically examine the influence of the geographic component on CD incidence rates.

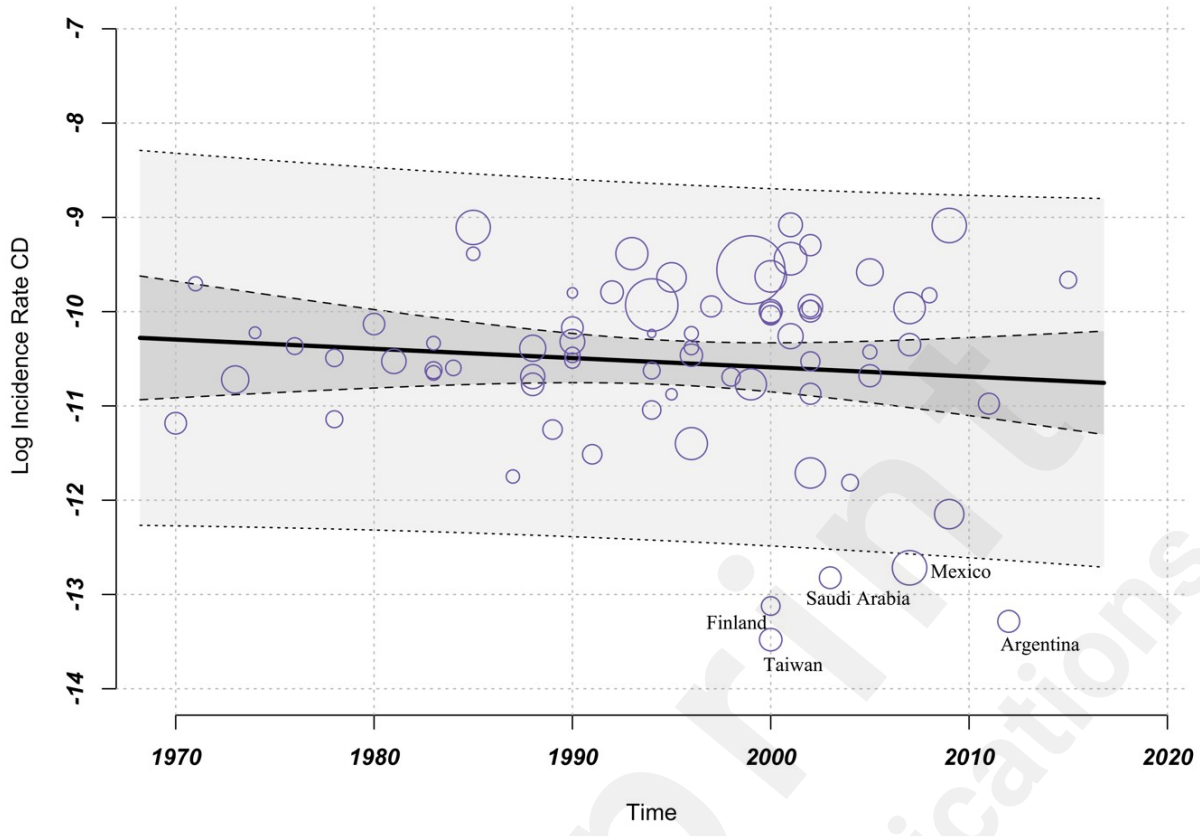

Figure 2: ***Meta-regression:*** *incidence over time: dependent variable incidence CD, independent variable time, Bubbles symbolize the studies that have been included, with each bubble's size corresponding to the weighting assigned to the respective study (k=72, estimator: REML): Test of Moderators F-Test = 0,71 P=.39, I^2=97.85%, variance explanation via R^2 0.00%;*

Geographical and environmental factors as moderators of CD incidence rates

It is interesting to see that the highest mean incidence rates per 100,000 children and adolescents during the observation period from 1970 - 2019 were observed in Australia (11.12 new cases/10^5), Finland (6.31/10^5), Canada (7.12/10^5), Germany (6.15/10^5), and New Zealand (6.07/10^5). The lowest incidence rates were reported in studies from countries in Asia and South America. Strikingly, an incidence of CD almost twice as high was reported in Australia compared to the other included countries (Fig.3 and Forest-Plot Geographic variation in incidence rates of CD in Supplement). These data suggest geographic heterogeneity, which we first consider at the continental level.

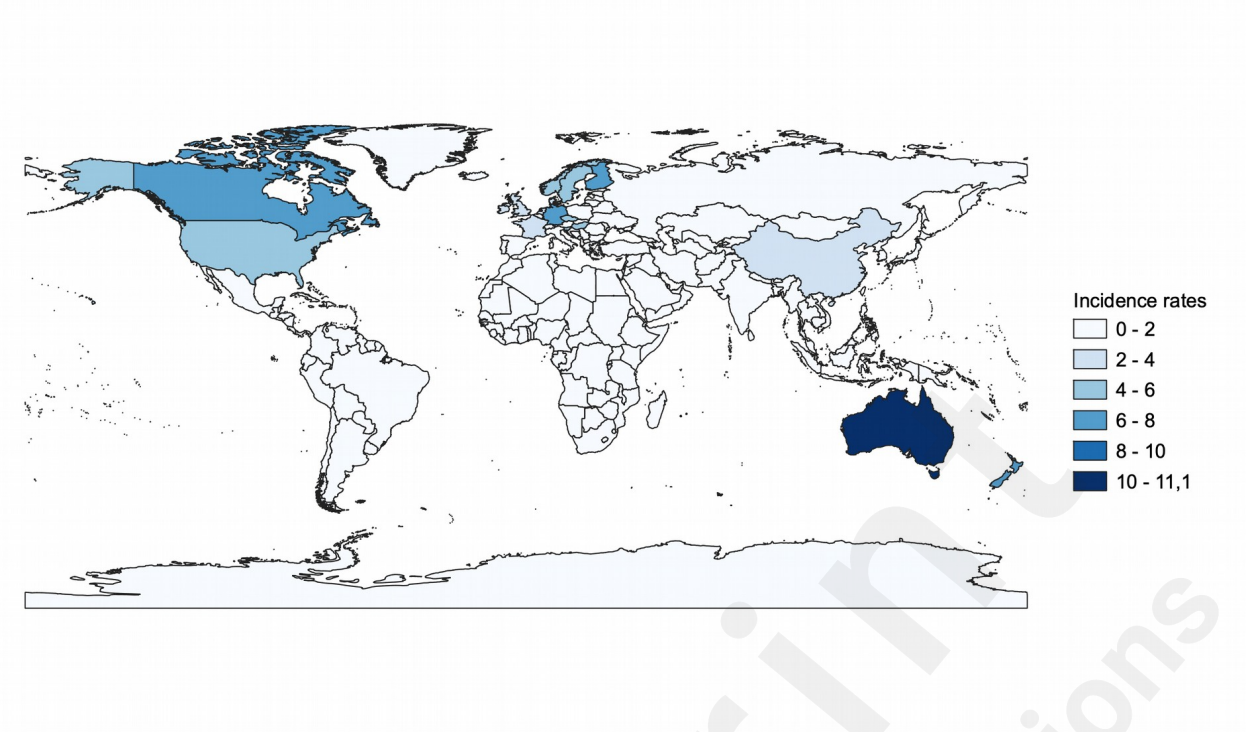

Figure 3: Geographical distribution of Crohn's disease incidence (raw data)

Indeed, a meta-regression with the variable *continents* indicated that 41.34 % of the heterogeneity can be explained. The test for moderators is significant (P <.001). Comparing this regression model with a more complex model in which we added the factor *time* to the moderator *continents*, an ANOVA showed no significant model improvement, confirming the notion that time does not act as a major moderator. In a further step, we examined the development of the incidence of Crohn's disease over time for each continent individually. The results of this analysis suggest that the incidence of Crohn's disease has developed differently in relation to the continents. Increasing trends were noted for North America, Europe, and Asia. For South America and Australia/Pacific-region, we found no confirmation of increasing incidence because of too few data points (see Fig. S9, Table S2 in the Supplementary Appendix).

The results also suggests that distance from the equator may have an effect on the incidence of CD. A corresponding meta-regression, which included *absolute distance from the equator* as a moderator, showed that CD incidence increased significantly with increasing distance from the equator (Fig. 4). Extrapolated to 1000 km, the incidence rate increased by 0.36%. The test for moderators yielded a significant result (P <.001). However, given the considerable heterogeneity in study results, distance from the equator formally contributed only moderately to better explain this variance (R^2 = 29.14%). (Table1, Fig. 4). We found similar results when we recalculated the analysis for the *country-specific UV index* instead of the *absolute distance from the equator*. The results show that incidence rates decrease with increasing UV exposure. The results with this factor were significant in the test of moderators (*P* < .001) and 18.57% heterogeneity was resolved (Table 1, Fig. 4). Given the correlation between the moderators of absolute distance from the equator and UVI (r = -0.87, *P* <.001), we refrained from a joint regression model to avoid problems of collinearity and unreliable coefficient estimates.

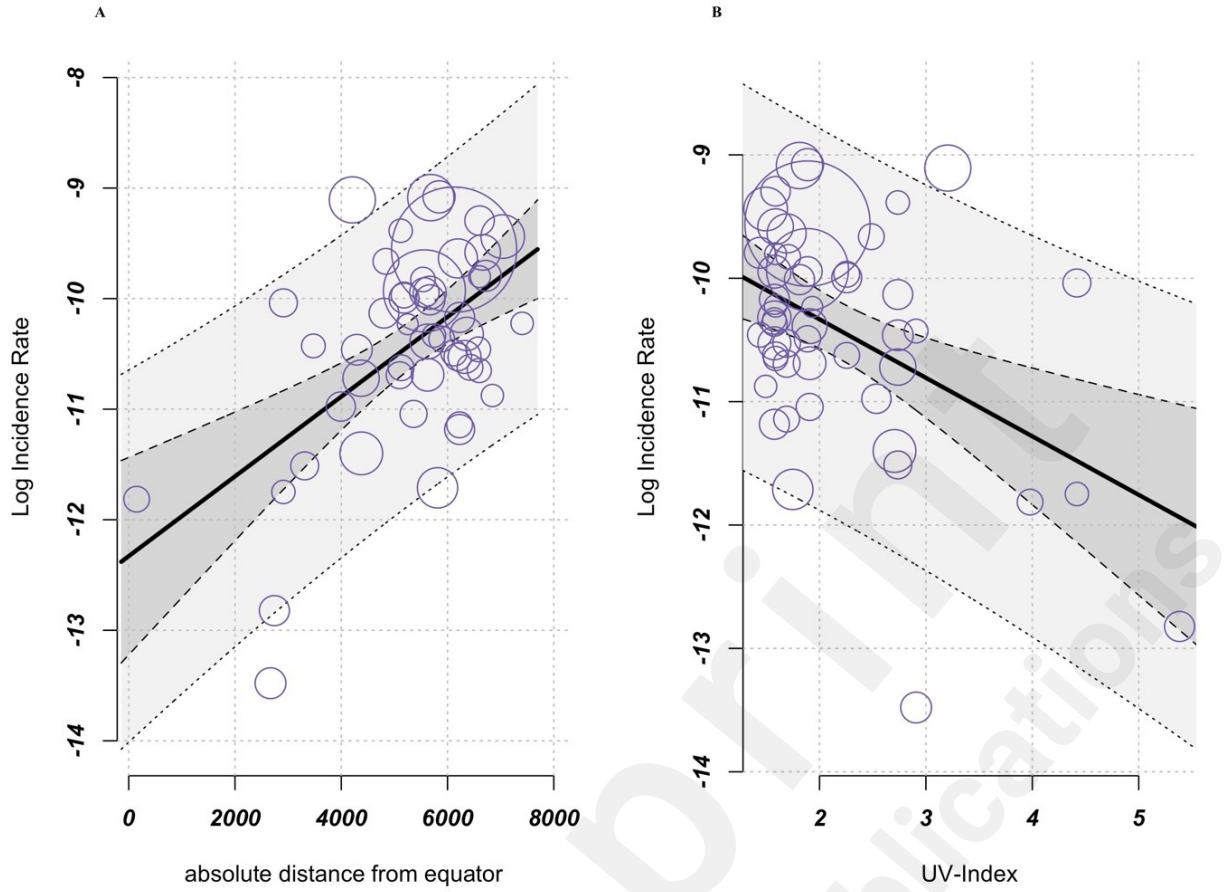

Figure 4: ***Meta-regression, A****: increasing incidence with increasing distance from the equator; variable incidence CD, independent variable absolute distance from equator (k=52, estimator: REML): Test of Moderators F-Test=18.78 P<.001, I^2=96.29%, variance explanation via R^2 29.14%,* ***B:*** *decreasing incidence with increasing UV-Index (UVI); variable incidence CD, independent variable UVI (k=52, estimator: REML): Test of Moderators F-Test=11.35 P<.001, I^2=96.94%, variance explanation via R^2 18.57%; Bubbles symbolize the studies that have been included, with each bubble's size corresponding to the weighting assigned to the respective study*

Table 2: ***Meta-regression results****: dependent variable incidences CD, independent variables: absolute distance to the equator (abs.Dis.) and ultraviolet radiation (UVI). ME Model (k=52, estimator: REML)*

Moderator	Estimate	SE	z-value	*P*-value	95% CI	I^2	R^2
abs.Dis.	0.0003	0.45	-27.06	<.001	0.0001 – 0.0005	96.29. %	29.14 %
UVI	-0.474	0.141	-3.37	<.001	-0.75 - -0.19	96.94 %	18.57 %

Socioeconomic factors as moderators of CD incidence rates

In a next step we investigated the extent to which socioeconomic factors could be considered moderators of heterogeneity. The results of the corresponding meta-regression showed that the *HDI*,

health expenditure as a percent of GDP, and the *UHC index* acted as moderators. Accordingly, the frequency of CD increases with increasing values of each moderator (Table 2, Figure 5). To avoid issues with collinearity and unreliable coefficient estimates resulting from the correlations between the socioeconomic factors, we decided not to use a joint regression model.

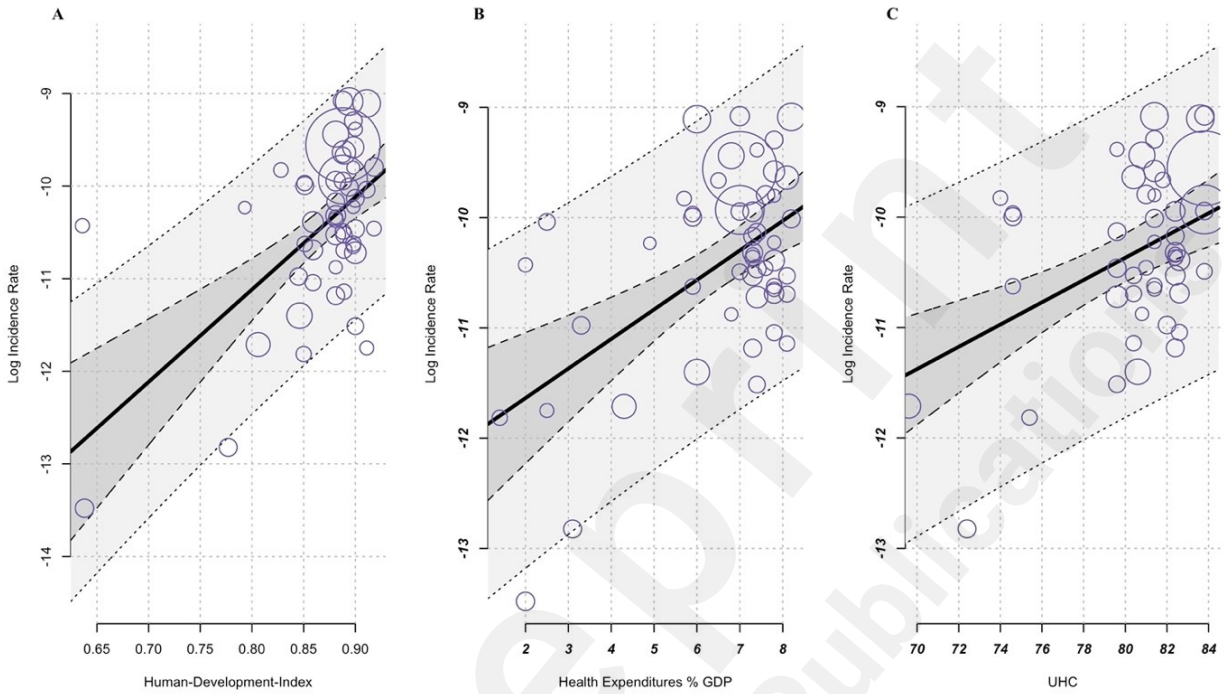

Figure 5: ***Meta-regression: A:*** *increasing incidence with increasing Human-Development-Index (HDI); variable incidence CD, independent variable HDI (k=52, estimator: REML): Test of Moderators F-Test=26.4 P<.001, I^2=95.87%, variance explanation via R^2 40.8%.* ***B:*** *increasing incidence with increasing health expenditure (CHE-GDP%); variable incidence CD, independent variable CHE-GDP% (k=52, estimator: REML): Test of Moderators F-Test=18.78 P<.001, I^2=96.53%, variance explanation via R^2 29.4%;* ***C:*** *increasing incidence with increasing UHC service coverage index SDG 3.8.1 (UHC); variable incidence CD, independent variable UHC (k=52, estimator: REML): Test of Moderators F-Test=17.27 P<.001, I^2=96.33%, variance explanation via R^2 28.86; Bubbles symbolize the studies that have been included, with each bubble's size corresponding to the weighting assigned to the respective study*

Table 3: ***Meta-regression results:*** *dependent variable incidences CD, independent variables: human development index (HDI), health expenditure as a % of GDP (CHE-GDP%), GDP, and UHC service coverage index SDG 3.8.1 (UHC) ME Model (k=52, estimator: REML)*

Moderator	Estimate	SE	z-value	*P*-value	95% CI	I^2	R^2
HDI	9.98	1.94	5.14	<.001*	6.18 – 13.79	95.87 %	40.8 %
CHE-GDP %	0.26	0.06	4.33	<.001*	0.15 – 0.39	96.53 %	29.4 %
GDP	<0.00	0.0004	-0.02	.98	-0.0001 – 0.0001	97.57%	<0.00%
UHC	0.1	0.02	4.12	<.001*	0.05 – 0.15	96.33%	28.86%

A multifactorial regression model to explain CD incidence rates

In our analysis, we identified different the widely independent factors *study timing*, *absolute distance from the equator*, and *HDI* or *UHC* as univariate moderators of CD incidence rates. To explain the high degree of heterogeneity between studies that we observed during the analyzed study period, we used a multifactorial meta-regression model that accounted for these complementary moderators as the final step of our investigation. As a result, the corresponding model showed a joint R2 of 62.5%, indicating that almost two-thirds of the heterogeneity can be explained by these three moderators. The test for moderators was significant at P <.001 (see Table 3).

Table 4: ***Meta-regression results****: dependent variable incidences CD, independent variables: Time, abs. distance from equator, Human Development Index (HDI): ME Model (k=52, estimator: REML): Test of Moderators F-Test=24.57, P<0.001*

Moderator	Estimate	SE	z-value	*P*-value	95% CI	I^2	R^2
multifactorial model: IR ~(Time + abs.Dis + HDI)							
Time	0.030	0.01	3.48	<.001	0.013 – 0.047		
Abs.Dis	0.0003	0.0001	3.69	<.001	0.0001 – 0.0004	92.99 %	62.56 %
HDI	9.50	1.84	5.15	<.001	1.914 – 10.153		

Discussion

Our systematic review with meta-analysis and meta-regression examined global trends in the incidence of CD. Although several individual studies reported an increase in incidence rates for CD in a certain (national) cohort, few high-quality studies were able to substantiate and quantify such an increase (Risk of Bias Analysis in Supplement). Furthermore, some of the studies reporting temporal trends in CD incidence rates were controversially discussed [1,6]. Different study designs also made it difficult to compare incidence rates over time, which may further contribute to the substantial heterogeneity in incidence rates.

In the present systematic review, we evaluated a total of 72 studies from 26 countries on the incidence of CD over a 50-year observation period. We found substantial heterogeneity in incidence rates, which was confirmed by meta-analysis using a random effects model (Cochrane Q= 3349.38, *P*<.001, I^2= 97.88%). Despite the large heterogeneity of the data, we obtained several interesting results. First, we found no clear evidence of a general global trend towards increasing CD incidence rates over time. While incidence rates might increase within individual countries, it rather appears that the inclusion of studies from a broader range of countries also increases the overall between-study heterogeneity to an extent that a global temporal trend is not identifiable. While incidence rates might increase within individual countries, it rather appears that the inclusion of studies from a broader range of countries also increases the overall between-study heterogeneity to an extent that a global temporal trend is not identifiable. This might be a result of differences in methodology and the

way in which the individual studies reported incidence rates over time and need further investigation in future research. The fact that little data was available in certain regions may also have contributed to the fact that a global trend over time was not discernible from our analyses. Kuenzig et al. (2021) reported similar issues in this regard. Due to the different reporting of incidence rates of IBD in childhood and adolescence they also had difficulties in describing a clear temporal trend [32]. Second, we observed a dependency of the incidence rates on the geographic location, with increasing incidence for countries that are further away from the equator. Third, we observed a similar effect for several socio-economic factors, in which higher scores correlated significantly with higher CD incidence rates.

Regarding the geographic differences in incidence rates of CD, several studies reported a north-south gradient. For example, Nerich et al. (2006) reported the effects of latitude on the geographic distribution of CD. However, quantification of the gradient by latitude was not performed [15]. Armitage et al. (2001) similarly reported a significant north-south gradient for CD in Scotland [33]. Because recent epidemiologic studies have reported an increasing incidence of IBD worldwide, including in southern countries, particularly also in the southern hemisphere [2,34], we decided to use absolute distance from the equator as a factor to represent and quantify a relationship between incidence and geographic location. The result of our meta-regression showed that incidence rates increased with increasing distance from the equator. This result corresponds with the results of our further analysis of possible moderators of incidence rates. We found that countries with a high UVI, other than Australia, have a lower incidence of CD. Our results correlate with findings from other studies showing that higher exposure to UV radiation, or sunlight, is associated with a lower risk of CD and IBD [16,35]. In our results, Australia stood out with a high incidence. Although Australia is considered sun-rich, 17% of Australian adolescents have vitamin D deficiency [35]. Vitamin D is formed in the skin when exposed to UV radiation. We therefore suspect a correlation between vitamin D status and the incidence of CD. Further studies should therefore examine in particular

whether a low vitamin D status is a risk factor for CD or IBD or a consequence. However, studies show that patients with IBD and especially CD also show a low vitamin D status and indicate a correlation with disease activity. Unfortunately, disentangling causality and correlation is an unresolved challenge in the ongoing debate about the interplay between Vitamin D and IBD [36–38]. Although latitude or absolute distance from the equator and UV exposure are correlated, they cannot be fully replaced in our statistical analysis.

Our results concerning the socioeconomic factors contribute to the hypothesis that CD might correlate with industrialized, urbanized societies, largely due to a Western lifestyle and other associated environmental factors [13] which themselves go along with higher socioeconomic scores. It is also known that the incidence and prevalence of CD varies between countries with different HDI [39–41]. Although there are few epidemiologic studies of CD in underdeveloped and developing countries, the incidence of CD is increasing significantly worldwide, affecting even countries previously considered to be at low risk [34,42]. It has been observed that the incidence and prevalence in developing countries is also increasing in children and adolescents, which has been attributed to the rapid modernization and Westernization of the population [13]. Our findings seem to follow a global pattern, namely that the process of industrialization has an impact on the incidence of CD. In this regard, we also follow the view of Takahashi et al. (2018) and Ananthakrishnan et al. (2015) that the level of development of countries and Western lifestyle are related to the level of incidence. However, causality cannot be inferred from our study. Further research is needed for this purpose. In recent times, there is a growing significance attributed to observational research conducted on real-world data (RWD), leading to the establishment of global research networks, exemplified by the Observational Health Data Sciences and Informatics (OHDSI) community. These networks aim to facilitate large-scale studies grounded in the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). Consequently, the use of observational studies that utilize RWD is a valuable way to study CD and IBD in the future [43].

Limitations

The study is limited by the use of two electronic databases for systematic literature search. Another limitation of the study is the exclusion of studies that were not published in English, Spanish, French, or German. Given that the included studies were mainly from countries with good access to the health care system (UHC >70), underreporting of countries with poorer access to the health care system should be discussed. We controlled the risk of publication bias using the Eggers regression test, rank correlation test, trim and fill analysis and fail-safe N analysis (Rosenberg method). Although these methods did not statistically indicate a bias due to publication bias, a small bias cannot be completely ruled out.

Conclusions

Based on available study data from 1970 to 2019 we could not identify a global, temporal trend towards increasing CD incidence rates, although these effects are reported for individual countries or regions. Instead we could demonstrate that the a substantial part of the observed heterogeneity between the published study results can be explained by the geographic location and by socioeconomic factors. Our study can be used to provide quantitative estimates of these trends for CD in childhood and adolescence. However, to establish causal relationships regarding potential risk factors, further studies are necessary, including those conducted in countries with lower levels of development. Nevertheless, our analysis provides valuable information to drive future research and health policies aiming to reduce the incidence of CD among children and adolescents. This needs continuous global monitoring of the incidence of IBD in childhood and adolescence to fully understand the trends in IBD incidence [32]. To this end, the implementation of internationally standardized and interoperable registries, coupled with the dissemination of health data via federated networks grounded on a CDM, such as the OMOP CDM, is deemed advantageous. The OMOP CDM aligns most closely with the requisites conducive to expediting data exchange within longitudinal

studies [43,44]. The utilization of such registries and data networks holds the potential to streamline the exhaustive and standardized accumulation as well as dissemination of data. This, in turn, would enhance our comprehension of CD and foster evidence-based approaches for preventive and interventional strategies.

Ethics and funding

A vote of the ethics committee was not required for this study because it was a systematic literature review and no patients were directly involved. The study was conducted without third-party funding or support.

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Data Availability

The data sets generated and/or analyzed during this study are available from the corresponding author upon reasonable request.

Statement on the use of generative AI

This manuscript was written and finalized by the authors without the help of an AI such as ChatGPT or other generative language models.

Author contributions

Conceptualization J.W., U.R., U.M.; methodology J.W.; systematic literature search and extraction J.W., U.M.; data analysis J.W., I.G.; writing—original draft preparation J.W.; writing—review and editing, I.G., U.M., I.R., F.B., J.K., U.R., F.D., M.A.; visualization J.W., F.B., I.R.; supervision J.K., I.G.; statistical supervision I.G.; administration J.W.; All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

All authors have contributed to the preparation of this publication voluntarily and free of charge. There are no conflicts of interest.

Abbreviations

abs.Dis	absolute distance from equator
CD	Crohn´s disease
CDM	Common Data Model
CHE-GDP%	health expenditure as a percentage of GDP
GDP	Gross Domestic Product
HDI	Human Development Index
IBD	Inflammatory bowel disease
REML	Restricted maximum likelihood
RWD	Real World Data
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
UC	ulcerative colitis
UHC	UHC service coverage index SDG 3.8.1

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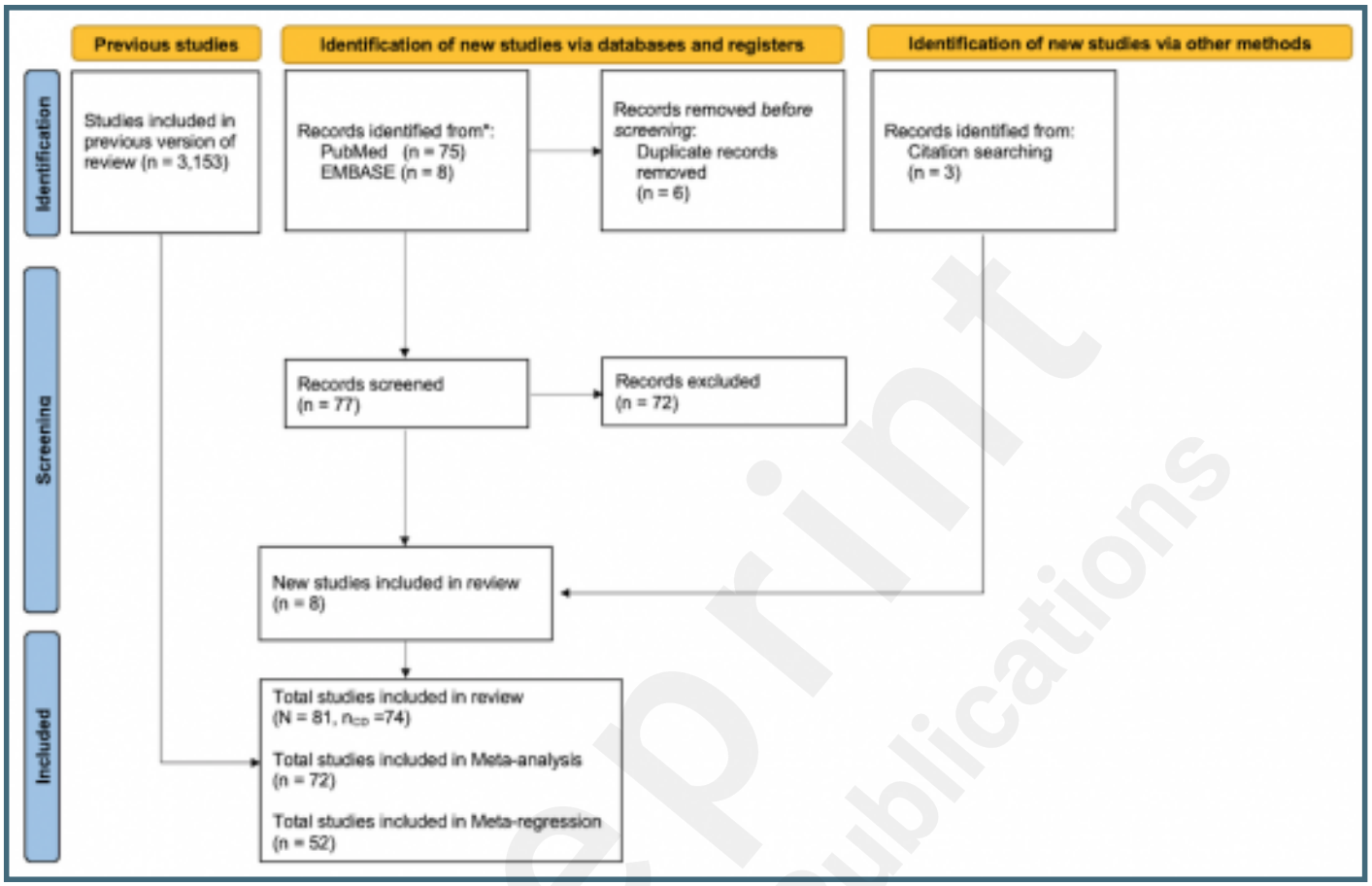
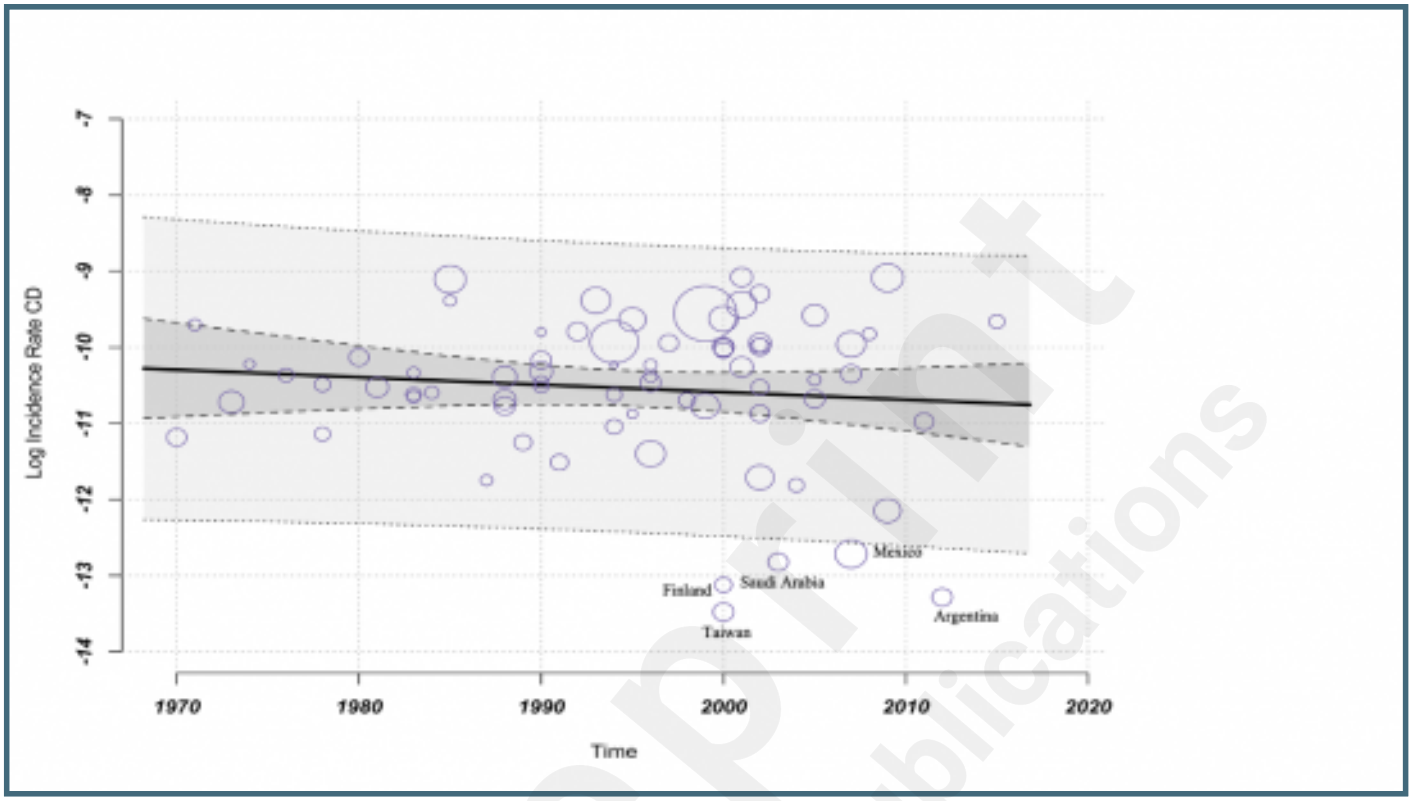
Supplementary Files

Figures

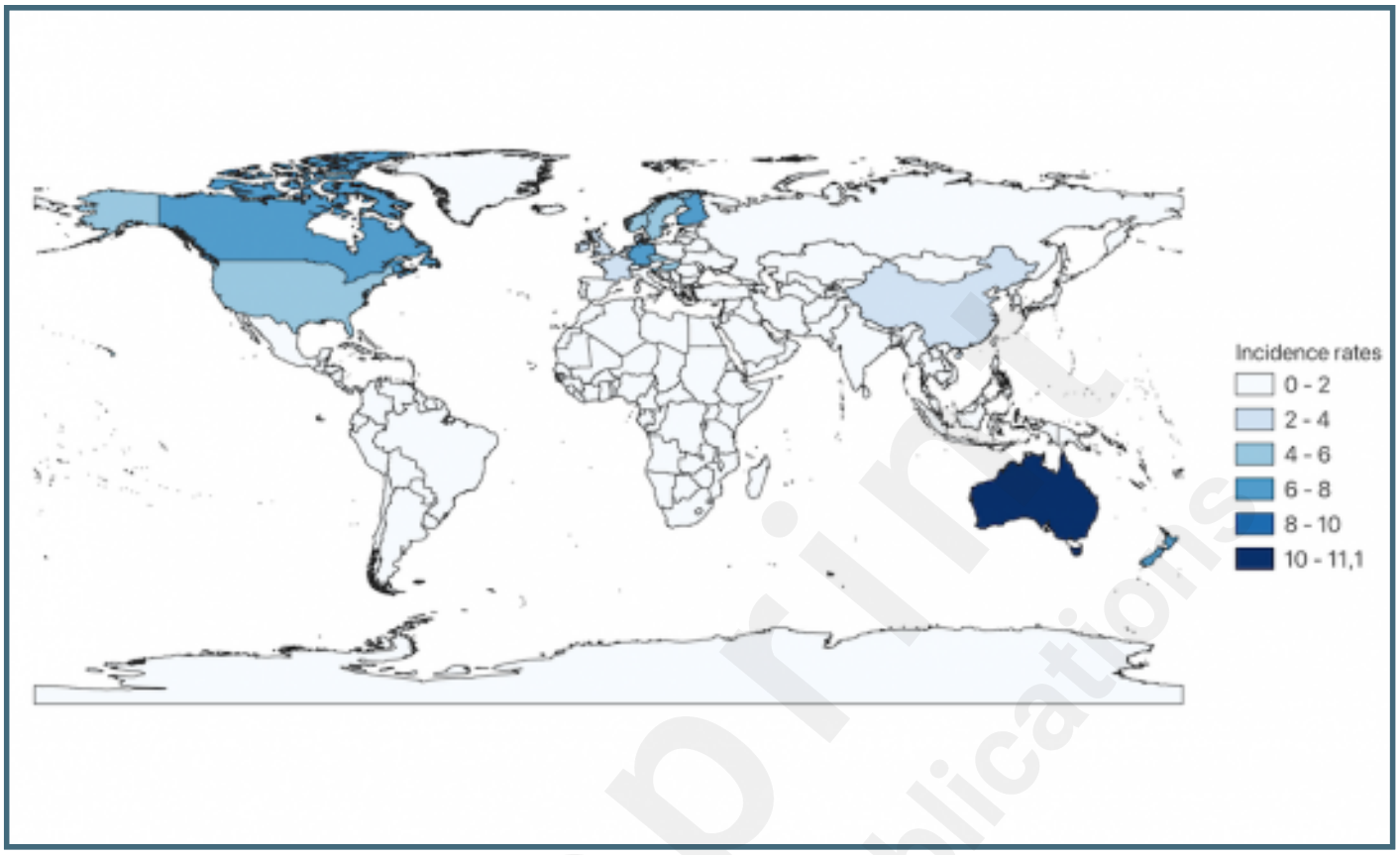
PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases, registers and other sources [31], for our systematic review with meta-analysis and meta-regression.

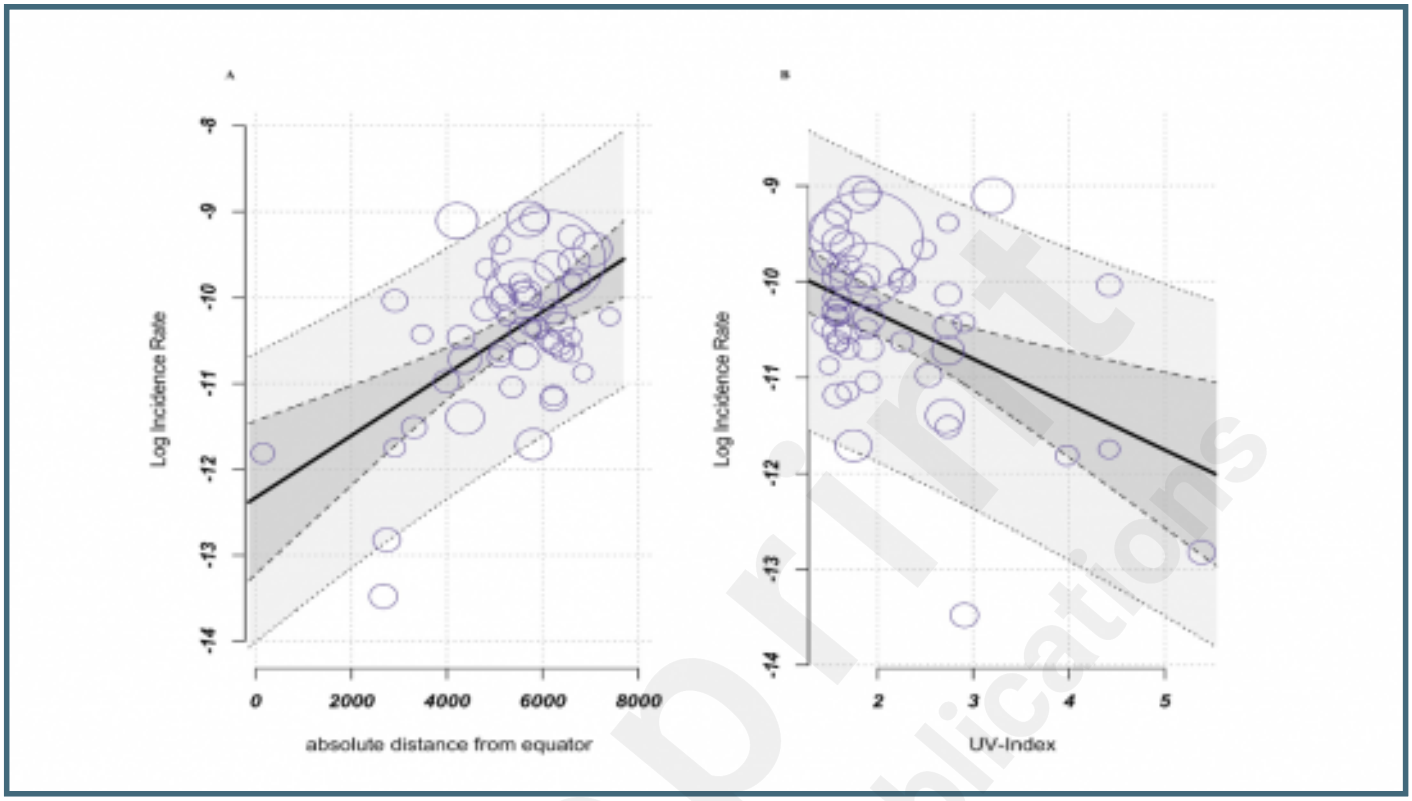


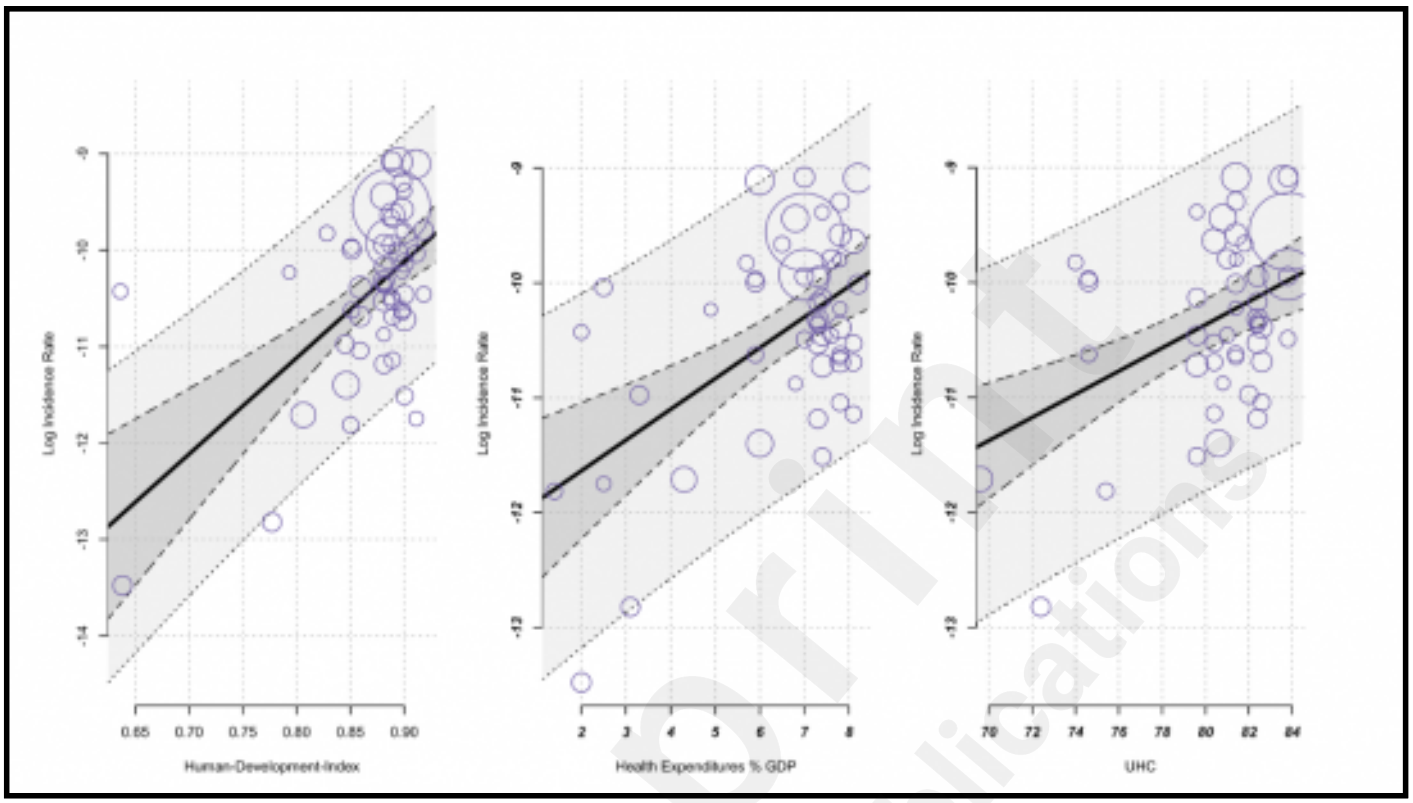
Meta-regression: incidence over time: dependent variable incidence CD, independent variable time, Bubbles symbolize the studies that have been included, with each bubble's size corresponding to the weighting assigned to the respective study (k=72, estimator: REML): Test of Moderators F-Test = 0,71 P=.39, I2=97.85%, variance explanation via R2 0.00%;.



Geographical distribution of Crohn's disease incidence (raw data).







Multimedia Appendixes

Search strategy systematic literature search in Pubmed and Embase via Ovid.
URL: http://asset.jmir.pub/assets/ae237340bb0055e5edae6e8346426c98.pdf

Supplement References of the found studies.
URL: http://asset.jmir.pub/assets/e9d16011b9024f7faa0d963563b97544.pdf

Summary of the included studies.
URL: http://asset.jmir.pub/assets/04a542248f6faa9124e766ca1dbd7202.pdf

Risk of Bias analysis.
URL: http://asset.jmir.pub/assets/f70e8a813a0c7376dd25d2773bae0ee2.pdf

PRISMA checklist.
URL: http://asset.jmir.pub/assets/fb6b035f701638e146f965a2be3b89fe.pdf

Fig. S. 1: Forrest Plot Meta-analysis across all studies on the log scale; Random-Effects Model (k = 72; tau2 estimator: REML).
URL: http://asset.jmir.pub/assets/a04fc8de9f2ad8e0a2a2cb3007dcd444.png

Subgroup analysis incidence CD in 10-year steps: Forest Plot pooled incidence rates per 10 years; Random-Effects Model (k = 5; tau2 estimator: REML).
URL: http://asset.jmir.pub/assets/dbb205eb2e3166b277470ddf0f57980c.png

Supplement Subgroup analysis incidence CD in 10-year steps: Forest Plot Studies period 1970-1979; Random-Effects Model (k = 8; tau2 estimator: REML).
URL: http://asset.jmir.pub/assets/e66bc4c079f8e12782a994fc2a559693.png

Supplement Subgroup analysis incidence CD in 10-year steps: Forest Plot Studies period 1980-1989; Random-Effects Model (k = 16; tau^2 estimator: REML).
URL: http://asset.jmir.pub/assets/0fd795abd4e698fb5ec73c0a9b0b8bf4.png

Supplement Subgroup analysis incidence CD in 10-year steps: Forest Plot Studies period 1990-1999; Random-Effects Model (k = 25; tau^2 estimator: REML).
URL: http://asset.jmir.pub/assets/19b27933563537a50d6846e5a9d851f0.png

Supplement Subgroup analysis incidence CD in 10-year steps: Forest Plot Studies period 2000-2009; Random-Effects Model (k = 33; tau2 estimator: REML).
URL: http://asset.jmir.pub/assets/c9c1f0b2caf2ef7fbdf9215ccd7b03a1.png

Supplement Subgroup analysis incidence CD in 10-year steps: Subgroup analysis: Forest Plot Studies period 2010-2019; Random-Effects Model (k = 12; tau2 estimator: REML).
URL: http://asset.jmir.pub/assets/ee99b8603ffd425353a04bcaf1c90fe2.png

Geographic variation in incidence rates of CD: Forest plot pooled incidence rates CD by continent; Random-Effects Model (k =

5; tau2 estimator: REML).
URL: http://asset.jmir.pub/assets/cecb392ea192578c1fbb387406e93b77.png

Meta-regression, Subgroups Continents, dependent variable incidence CD, independent variable: Time, Bubbles symbolize the studies that have been included, with each bubble's size corresponding to the weighting assigned to the respective study.
URL: http://asset.jmir.pub/assets/d2f34fb6206a33e253c119e80343999c.png

Meta-regression results: dependent variable incidences CD, independent variables: Time, 1 too few observations for regression analysis, pooled IR 0.23/105 (on log scale -12.96), a multiplicative change factor > 1 increasing IR, < 1 decreasing IR.
URL: http://asset.jmir.pub/assets/a3ae71691e3219be219747132cb0fef9.pdf