Heat Waves, Incidence of Infectious Gastroenteritis, and Relapse Rates of Inflammatory Bowel Disease: A Retrospective Controlled Observational Study

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OBJECTIVES: **The objective of this study was to evaluate the effect of heat waves on flares of inflammatory bowel disease (IBD) and infectious gastroenteritis (IG).**

METHODS: **In this retrospective controlled observational study, data from 738 IBD and 786 IG patients admitted to the University Hospital of Zurich in the years 2001–2005, as well as from 506 other noninfectious chronic intestinal inflammations, which were used as control, were collected. Climate data were obtained from the Swiss Federal Office for Meteorology and Climatology.**

RESULTS: **The presence of a heat wave increased the risk of IBD flares by 4.6% (95% confidence interval (CI): 1.6–7.4%, $P=0.0035$) and of IG flares by 4.7% (95% CI: 1.8–7.4%, $P=0.0020$) for every additional day within a heat wave period. In the control group there was no significant effect (95% CI: −6.2–2.9%, $P=0.53$). Screening of alternative forms for the effect of heat waves suggested that for IG the effect is strongest when lagged by 7 days (risk increase per day: 7.2%, 95% CI: 4.6–9.7%, $P<0.0001$), whereas for IBD no such transformation was required. Other formulations with additive effects, interactions between heat waves and time of the year, and additional adjustments for daily average temperature did not show any improvement in model fit.**

CONCLUSIONS: **In this retrospective controlled observational study, we found a substantial increase in hospital admissions because of flares of IBD and IG during heat wave periods. Whereas the effect on IG is strongest with a delay of 7 days, the effect on IBD flares is immediate, suggesting different mechanisms.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Instrumental observations of global temperature evolution reveal a pronounced warming during the past 150 years. One expression of this warming is the observed increase in the occurrence of heat waves as it has been reported for the record-breaking central European summer temperatures in 2003 (1).

Climate change affects human health through multiple pathways, including direct effects and indirect effects that operate through changes in the range of disease vectors, water quality, or air quality (increase of airborne pollen or new allergenic pollen in certain regions) (2). The health impact of heat waves has been reported several times during the past decades, not only in European countries but all around the world. In 1999, ~500 deaths were attributed to a heat wave in Chicago (3,4), and up to 30,000 to 70,000 additional deaths occurred during the European 2003 heat wave, particularly in France and Germany (5–7). An estimated 7% increase in all-cause mortality occurred in Switzerland during the months June to August 2003 (5). The increase in mortality during heat waves is known to be higher in urban areas. This might be caused by a more distinctive urban–rural contrast with regard to heat stress related to a higher population density or a nightly pronounced urban heat island effect (8).

Although there have been several reports on increase in mortality, only scarce information exists on the impact of temperature

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increase on morbidity. In one French report, medical records of 726 patients aged >65 years who had been admitted to the emergency department during August 2003 were reviewed. In 42 patients, heat-related illnesses were retrospectively diagnosed, of which not even one had been diagnosed in the primary evaluation (9). Another study identified cardiac troponin I as an independent risk factor for severe myocardial damage among patients with heat-related illnesses, associated with significantly decreased 1-year survival (10). A French nested cross-sectional study reported an 8.8% increase of self-reported health deterioration and a 7.8% increase of objective morbidity among the elderly after the August 2003 heat wave (11).

However, information on the impact of heat waves on young patients and typical young patients' illnesses, such as inflammatory bowel disease (IBD), is rare. IBD has two major forms: ulcerative colitis (UC) and Crohn's disease (CD). They are characterized by relapsing inflammation of the gastrointestinal tract with potential extraintestinal manifestations and are defined by various clinical, pathological, endoscopic, and radiologic features (12). A genetic predisposition has been demonstrated to have an important effect on the development of IBD, especially CD (13). Although genetic factors are believed to account for ~50% of new cases of IBD, environmental factors are also considered important for the etiology of CD and UC (13).

Several studies have identified seasonal variation in the clinical course of IBD patients. Some studies report an increase in relapses during autumn and winter in CD patients (14), whereas other studies report a contrary result, suggesting an increase during spring and summer (15). In UC studies claiming a seasonal impact, there are conflicting results as well, reporting both an increase during spring and summer (16) and during winter (17).

In this retrospective study we evaluate the influence of heat waves on incidence of hospital admissions due to IBD. Within the investigated time period, the accumulation of heat waves during the 2003 summer gave us the opportunity to record several heat waves to be compared with time periods without heat waves. As there have been several reports on an influence of the development of IBD by enteric pathogens (18), and as there have additionally been reports on the influence of enteric microbial infections like Salmonellosis or Campylobacteriosis by climate changes, we also assessed the incidence of infectious gastroenteritis (IG). Other noninfectious chronic intestinal inflammations (NIIs) have been used as control group.

METHODS

Study population

All patients who were admitted to the University Hospital of Zurich with symptoms leading to the final diagnosis of IBD, IG, and NII from 1 January 2001 through 31 December 2005 were eligible for the study. Patients were selected from an administrative database providing information about age, date of hospital entry, and discharge. Furthermore, the database provided the International Classification of Diseases version 10 (ICD-10) (19) codes for final hospital diagnoses. Patients with CD (ICD-10: K50.0-9), UC (ICD-10: K51.0-9), and NII (ICD-10: K52.0-9) as well as IG (ICD-10: A00.0-A09.0) were enrolled. To validate the data, we reviewed a random sample of 228 out of all 2,030 patients. Of this sample, two ICD-10 codes were incorrectly encoded. As Zurich and its environment are frequently visited by tourists, we also reviewed the sample for hospital admissions of tourists. Only 1 out of the 228 reviewed patients was a tourist.

Climate data

Meteorological data were collected at the meteorological station Zürich-Fluntern, 556 m above sea level. The air temperature is measured 2 m above ground level according to the recommendations of the World Meteorological Organization. The meteorological data were collected with an automatic weather station and aggregated on a daily basis for the study period 2001–2005.

Heat wave definitions

For this study we used the definition of heat wave recommended by the World Meteorological Organization, classifying any period of 6 days with maximum temperature >5 °C (9 °F) above the daily average maximum temperature to be a heat wave (20). To assess a possible cumulative effect of heat waves on hospital admissions, we used the day within a heat wave period as a possible predictor for disease incidence. Alternatively, a simple additive effect of a heat wave has also been investigated.

Statistical analysis

We employed Poisson regression (21) to compute relative risk estimates for the effect of heat waves on daily incidence of IBD, IG, and NII, respectively. The 95% profile likelihood confidence intervals (CIs) for the relative risk and associated *P* values based on the likelihood ratio test statistic have been computed. We adjusted our risk estimates for day-of-the-week effects (with 7 categories, treating public holidays as Sundays), long-term time trends (assumed to be linear), and yearly seasonal patterns (assumed to follow a sine–cosine form) (22). The analysis is automatically controlled for age, sex, and other patient-specific characteristics, similar to the self-controlled case series method (23,24), because the time-dependent exposure variables are common to all patients. With regard to the lagged effect of heat waves, we analyzed models considering a lagged effect of a heat wave on daily incidence of up to 14 days. To investigate whether the heat wave effect interacts with the time of the year, we included an interaction between the heat wave predictor and the seasonal pattern. Similarly, interactions between heat wave and sex and between heat wave and age group (<25, 25–65, and >65 years) have been considered. Screening of alternative formulations such as lagged effects of heat waves and additional adjustments for daily average temperature has been done using the Bayesian information criterion. The Bayesian information criterion, a consistent model selection criterion that penalizes model complexity stronger than the Akaike information criterion, has been used to avoid overfitting (25). Statistical analyses were performed using the R software (26).

RESULTS

During the study period 2001–2005, a total of 738 IBD patients aged 15–94 years, 786 IG patients aged 0–96 years, as well as 506 patients aged 0–94 years suffering from NIIs were admitted to the University Hospital of Zurich. A total of 17 heat waves, according to the World Meteorological Organization definition, were identified in that period, with length of up to 19 days (30 May to 17 June 2003).

Results from several Poisson regression models are shown in **Table 1**. For each disease group (IBD, IG, NII), the estimated effect of heat waves adjusted for day-of-the-week, long-term time trends, and seasonal pattern is given. There is evidence for an increase of IBD hospital admissions by 4.6% (95% CI: 1.6–7.4%, $P=0.0035$) for each additional day within a heat wave period. Presence of a heat wave was estimated to increase the risk of IG by 4.7% for every additional day within a heat wave period (95% CI: 1.8–7.4%, $P=0.002$). In the control group there was no evidence for a heat wave effect (risk increase per day: −1.4%, 95% CI: −6.2 to 2.9%, $P=0.53$). The alternative additive formulation showed an increase of 34.4% (95% CI: 6.6–67.4%) and 34.8% (95% CI: 7.3–67.3%) for IBD and IG, respectively, during heat wave periods.

Table 2 shows that this additive formulation provided a slightly inferior fit according to the Bayesian information criterion. Lagging the cumulative effect of heat waves revealed that a 7-day lag considerably improved the fit for IG but not for IBD or NII (see **Supplementary Material** online). For this lag, the risk increase of IG hospital admissions was estimated to be 7.2% (95% CI: 4.6–9.7%, $P<0.0001$) for each additional day within a heat wave period (compare **Table 1**).

Formulations with additional adjustments for daily average temperature did not show any improvement in model fit (compare **Table 2** and **Supplementary Material**) online. Including an interaction between the heat wave predictors and the seasonal pattern did not change the results significantly ($P=0.56$ for IBD, $P=0.64$ for IG, and $P=0.35$ for NII; see also **Table 2** and **Supplementary Material** online). We also included an interaction between heat wave predictors and sex as well as heat wave predictors and age groups. Regarding IBD flares, there was some weak evidence for an interaction between heat wave predictors and sex ($P=0.029$), with an increase to 7.5% (95% CI: 3.6–11.1%) for females (see **Supplementary Material** online). In this formulation, the effect for females decreases to 0.9% (95% CI: −4.1 to 5.4%). There was, however, no evidence for this interaction

Table 1. Increase in hospital admissions during heat waves for inflammatory bowel disease (IBD), infectious gastroenteritis (IG), and other noninfectious intestinal inflammations (NIIs)

	RR	95% CI	*P* value
IBD			
Increase per day	1.046	1.016–1.074	0.0035
Increase (additive)	1.344	1.066–1.674	0.013
Increase per day (7-day lag)	1.016	0.983–1.047	0.34
IG			
Increase per day	1.047	1.018–1.074	0.002
Increase (additive)	1.348	1.073–1.673	0.011
Increase per day (7-day lag)	1.072	1.046–1.097	<0.0001
NII			
Increase per day	0.986	0.938–1.029	0.53
Increase (additive)	1.085	0.794–1.448	0.60
Increase per day (7-day lag)	1.002	0.958–1.041	0.94

CI, profile likelihood confidence interval; RR, relative risk.

Table 2. BIC for various models

Exposure	IBD		IG		NIIs	
	BIC	ΔBIC	BIC	ΔBIC	BIC	ΔBIC
–	2,929.5	1.0	3,167.2	19.6	2,390.7	0
Heat wave	2,928.5	0	3,165.1	17.5	2,397.8	7.1
Heat wave (additive)	2,930.9	2.4	3,168.2	20.6	2,397.9	7.2
Heat wave (7-day lag)	2,936.1	7.6	3,147.6	0	2,398.2	7.5
Average temperature	2,934.2	5.7	3,174.7	27.1	2,397.5	6.9
Heat wave + average temperature	2,935.7	7.2	3,170.5	22.9	2,404.0	13.3
Heat wave *season	2,942.4	13.8	3,179.2	31.6	2,410.7	20.0
Heat wave (additive) *season	2,945.2	16.6	3,183.0	35.4	2,409.3	18.7
Heat wave (7-day lag) *season	2,950.0	21.5	3,151.5	3.9	2,411.8	21.1

BIC, Bayesian information criterion; IBD, inflammatory bowel disease; IG, infectious gastroenteritis; NII, noninfectious intestinal inflammation.
Models with interaction terms between the heat wave variable and the seasonal pattern are indicated by the asterisk. All models include a day-of-the-week effect (including holidays), a linear trend, and a seasonal component. The difference in BIC (ΔBIC) is given in comparison with the best fitting model.

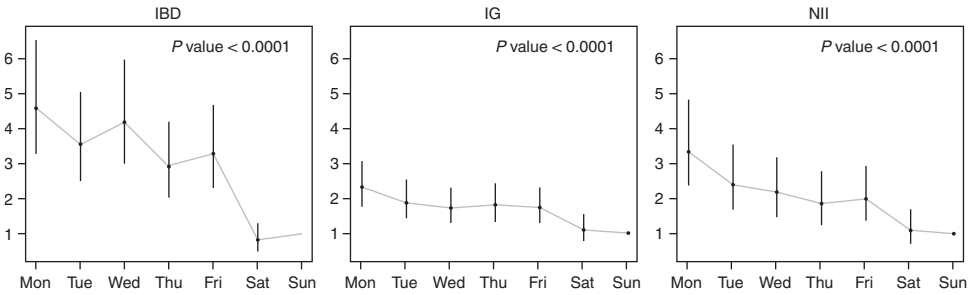

Figure 1. Day-of-the-week effects in hospital admissions because of flares of inflammatory bowel disease (IBD), infectious gastroenteritis (IG), and other noninfectious intestinal inflammations (NIIs). Shown are relative risks (RR) with 95% profile likelihood confidence intervals and overall *P* values. Sundays are taken as reference category.

for IG ($P=0.52$) or NII ($P=0.75$) (see **Supplementary Material** online). Including an interaction between heat wave effect and age group also did not change the results significantly ($P=0.92$ for IBD, $P=0.65$ for IG, and $P=0.58$ for NII; see also **Supplementary Material** online).

Admittance because of flares of IBD showed substantial day-of-the-week variation with higher incidence on week days (compare **Figure 1**). A similar, but slightly less pronounced, day-of-the-week pattern can be seen for IG and NII. Hospital admissions increased by 14% (95% CI: 8–20%, $P<0.0001$) and 20% (95% CI: 13–28%, $P<0.0001$) in each year for IBD and NNI, respectively, but no such evidence for a trend was seen for IG (95% CI: −7 to 3%, $P=0.38$). There was weak evidence for a yearly seasonal pattern peaking in winter for IG ($P=0.052$), but not for IBD ($P=0.70$) and NNI ($P=0.17$).

DISCUSSION

Climate change affects the health of populations in many ways. Some impacts will become evident before others. Some will occur via direct pathways (heat waves and death), and others will occur via indirect pathways entailing disturbances of natural ecological systems (e.g., mosquito population range and activity or new aeroallergens). Some other impacts might occur via a combination of both as suggested by this study.

In this first study on the impact of climate change—represented by an increasing number of heat waves—on diarrheal diseases in industrialized countries, we identified a cumulative effect of heat waves on hospital admissions because of IBD and IG flares. After adjustment for temporal and seasonal trends, hospital admissions are estimated to increase by 3.7% and 5.0% for IBD and IG, respectively, for each additional day of a heat wave period. For IG admissions, an even more pronounced increase of 7.7% can be seen if a 7-day delayed effect of heat waves is considered. This indicates that the effect of heat waves on IG flares occurs with a 1-week delay, whereas it is immediate with respect to flares of IBD.

What factor(s) could relate heat waves to flares of IBD and IG and explain our findings? On one hand, it is obvious that environmental bacterial growth conditions are dependent on air, soil, and water temperature. During a heat wave, changes in bacterial composition of food, skin, soil, and water may occur. This has never been investigated in much detail. However, recent research suggests that temperature plays a crucial role for the expansion of enterohemorrhagic *Escherichia coli* and other pathogenic bacteria. For our findings on infectious gastroenteritis, a simple explanation would be that heat waves favor the expansion of potential pathogenic bacteria and/or viruses. This is supported by the finding that the effect of a heat wave was maximized by a 7-day lag, suggesting infectious gastroenteritis requiring some lag time to develop. A similar effect was described in a study by Zhang *et al.* (27) in 2008. They reported on the effect of weather on the transmission of bacterial dysentery in China. Maximum temperature 1 month before was one major risk factor for an increase in the incidence of dysentery. However, a clear limitation of our study preventing similar conclusions is the lack of data to differentiate between viral and bacterial intestinal infections for IG patients.

There are a number of further limitations of our study. Even though we controlled for potential confounders as age and gender, we were not able to control for all potential confounders, e.g., smoking status. As smoking habits might change during heat waves, and as these changed smoking habits might especially influence flares in IBD patients, this might be a potential confounder. Moreover, we were not able to adjust for other time-dependent exposure variables, e.g., humidity. We also had no detailed data on the patient-level exposure to heat, which might run the risk of an ecological fallacy. Additional multiregional studies will be required to underline our findings. Another limitation of the study is a potential risk of misclassification of cases because of retrieving data from a database. However, to quantify this risk, we reviewed ~10% of the cases and only in a very small portion a misclassification was found. Nevertheless, generalizability of the results of this single-center study to other regions still needs to be investigated. Finally, there are potential limitations of our control group

as some noninfectious inflammations of the intestine might be the result of misclassification and might correctly need a classification as IBD or IG. However, we could not find evidence for this during very detailed chart review of ~25% of the cases included in our analysis.

Altered environmental bacterial growth conditions might also contribute to the observed increase in the number of IBD flares. Recent research suggests that genetic susceptibility factors for the pathogenesis of IBD are mainly located in genes/proteins of the innate immune response dealing with our intestinal microbiota (28). Genetic variants of bacterial receptors or pattern recognition receptors such as NOD2 or TLR5 or genes involved in the intracellular processing of invading bacteria such as *ATG16L1* or *IRGM* have been shown to be important risk factors for IBD (28). This indicates that a change in bacterial compositions challenging this innate immune response could well play a role for disease flares and symptoms. However, in contrast to IG there was no delay between the onset of heat waves and the increased risk of IBD flares.

Another explanation would fit better with the immediate effect of heat waves on IBD flares: heat waves are known to cause physical stress to humans as evident from increased frequencies of other stress-dependent health events such as heart attacks (10). Physical as well as mental stress have been shown to cause flares of IBD (29) and may explain the increase in IBD hospital admissions during heat waves. However, besides the possibility of heat waves triggering flares of IBD, it might also only worsen a clinically not apparent underlying flare. With our observational study design, it is not possible to discriminate between the two effects, and additional studies on that hypothesis are required.

Keeping in mind that the rate of heat waves is likely to increase in Europe, the possible impact on health becomes more important. This is underlined by the already mentioned new global climate model considering the major urban impact (8), as almost half of the world's population is living in urban areas (30). Finally, this also indicates that the impact of climate change on health has a relevant economic aspect. Therefore, mitigation and adaptation strategies are needed to reduce current vulnerability to climate change and to address the health risks projected to occur over the coming decades.

CONFLICT OF INTEREST

Guarantor of the article: Christine N. Manser, MD.

Specific author contributions: Christine N. Manser: data collection, data interpretation, literature search, and writing; Michaela Paul: data analysis, data interpretation, figures, and writing; Gerhard Rogler: study design, data interpretation, and writing; Thomas Frei: study design, data interpretation, and writing; Leonhard Held: study design, data analysis, data interpretation, figures, and writing.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Heat waves can affect mortality, especially among the elderly.
- ✓ There are seasonal variations in the clinical course of inflammatory bowel disease (IBD).
- ✓ Enteric microbial infections might additionally be influenced by climate changes.

WHAT IS NEW HERE

- ✓ Heat waves significantly increase the risk of IBD flares compared with controls.
- ✓ Heat waves significantly increase the risk of infectious gastroenteritis compared with controls.
- ✓ The impact of heat waves on infectious gastroenteritis is strongest for a 7-day time lag.

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