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Relative risk of irritable bowel syndrome following acute gastroenteritis and associated risk factors

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SUMMARY

A prospective cohort study using electronic medical records was undertaken to estimate the relative risk (RR) of irritable bowel syndrome (IBS) following acute gastroenteritis (GE) in primary-care patients in The Netherlands and explore risk factors. Patients aged 18–70 years who consulted for GE symptoms from 1998 to 2009, met inclusion/exclusion criteria and had at least 1 year of follow-up data were included. Patients with non-GE consultations, matched by age, gender, consulting practice and time of visit, served as the reference group. At 1 year, 1·2% of GE patients ($N=2428$) had been diagnosed with IBS compared to 0·3% of the reference group ($N=2354$). GE patients had increased risk of IBS [RR 4·85, 95% confidence interval (CI) 2·02–11·63]. For GE patients, concomitant cramps and history of psycho-social consultations were significantly associated with increased risk. GE patients had increased risk of IBS up to 5 years post-exposure (RR 5·40, 95% CI 2·60–11·24), suggesting there may be other contributing factors.

Key words: Gastroenteritis, infectious disease epidemiology, irritable bowel syndrome.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder (FBD) characterized by episodic abdominal pain and altered bowel habits that affects ~12% of the global population [1–3]. The aetiology, pathogenesis and prognosis of IBS are not well understood and there is no widely effective treatment [4–9]. IBS causes significant morbidity, places substantial burden on healthcare systems and can greatly affect quality of life [10–17]. In the USA, IBS accounts for 2·4–3·5 million physician visits annually, costing an estimated US$30 billion [13]. In The Netherlands, the annual disease burden of post-infectious (PI)-IBS associated with *Campylobacter* spp. and *Salmonella* spp. was recently estimated to be 2300 disability-adjusted life years (DALYs), potentially accounting for nearly 50% of the total burden for these pathogens [10].

There is increasing evidence that acute infectious gastroenteritis (GE) can increase the risk of IBS,

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with several studies demonstrating that a significant number of GE patients develop PI-IBS [1, 2, 18–23]. *Campylobacter, Shigella, Salmonella* and *Escherichia coli* infections as well as viral agents, including norovirus, and parasites have been associated with PI-IBS [5, 21, 23–25]. It has been hypothesized that exposure to an infectious organism alters gut flora, increases intestinal permeability and triggers chronic inflammation, inducing PI-IBS [3, 9, 26, 27].

Studies of PI-IBS incidence and risk factors have yielded varied results and few, if any, have identified unique causal infectious agent(s) [1, 2]. Severity of GE (duration of diarrhoea, presence of blood in stools, abdominal cramps, weight loss), younger age and female gender have been associated with increased risk of PI-IBS [21, 28–34]. Anxiety, depression and major life events have also been identified as potential risk factors with some hypothesizing that these disorders prolong gut inflammation and heighten sensory perception [22, 26, 28, 29, 32, 35–37]. Several studies have found increased healthcare-seeking behaviors in IBS patients but reasons for this are not well understood [15, 16, 33, 38]. Antibiotic use during or after GE has also been associated with increased risk of IBS [22].

Understanding the epidemiology of PI-IBS will contribute to a better understanding of the public health impact of the disease and potential preventive strategies. The primary purpose of this prospective cohort study is to estimate the relative risk (RR) of IBS following GE and explore potential risk factors in the Dutch primary-care population.

METHODS

A prospective cohort study was undertaken using electronic medical records from the Primary Care Network Utrecht (PCNU), a collaboration between Julius Centre of Utrecht University Medical Centre and 38 general practitioners (GPs) from six Utrecht primary-care centres. On average, 60 000 patients are seen annually with each patient being registered with a single practitioner. Routine healthcare data, including diagnosis, prescriptions and referrals, are recorded in a centralized database for all primary-care consultations. Diagnoses are coded using the 2nd edition of the International Classification of Primary Care (ICPC) from Wonca International Classification Committee (WICC). Prescribed medications are recorded using the World Health Organization's Anatomical Therapeutic Chemical (ATC) classifications.

The sample population was all PCNU patients, aged 18–70 years, seen between 1998 and 2009 with at least 1 year's electronic data. Patients with pre-existing diagnoses of cancer, alcohol abuse, inflammatory bowel disease, IBS, FBD or abdominal surgery, or $\geqslant 5$ prescriptions associated with IBS or FBD treatment were excluded from the analysis. Since GE symptoms may actually be undiagnosed IBS symptoms, patients with GE symptoms in the previous 12 months were also excluded.

Patients clinically diagnosed by their GP with GE during the observation period were identified as the index group (GE patients). Subsequent GE consultations within 30 days of the initial consultation were considered part of the same illness episode. To assess sensitivity, multiple definitions of GE were considered (Table 1) but only GE clinical results are presented. Patients were considered to have met a specific definition of GE if they had an exposure meeting that definition within 30 days of their original, matched exposure. Randomly selected PCNU patients consulting for non-GE symptoms, matched by age, sex and time of visit (within 1 month), served as the reference group (non-GE patients). Patients who developed IBS within the first 3 months were considered to be undiagnosed cases at study entry and were excluded.

The primary outcome of interest was IBS (Table 1). An incident case of IBS was defined to be a new diagnosis of IBS following GE exposure for GE patients and matched exposure for non-GE patients.

For GE patients, potential risk factors and comorbidities were evaluated: age at onset of GE, gender, socioeconomic status, bloody stools, abdominal cramps, weight loss, psychosocial factors, high consultation frequency and high prevalence of unexplained symptoms. Subjects were considered to have bloody stools, cramps or weight loss if they had an ICPC diagnostic code for these events within 7 days of the GE event. Consultations in the year prior to study entry with psychological (P category) or social problems (Z category) ICPC codes were used to identify psychosocial factors. Since consultations for fear or unexplained symptoms may indicate underlying psychosocial problems, ICPC diagnostic codes related to these events were also included (see online Supplementary Table S1).

It was determined that a sample size of 4206 per cohort group would provide at least 90% power, at a significance level of 0·05, to detect a RR for IBS of 2, which is a 100% increase.

Table 1. *ICPC codes selected for gastroenteritis (GE) and irritable bowel syndrome (IBS)*

	ICPC code	Diagnosis	1998–2009 events*
GE (confirmed)	D70	Gastrointestinal infection	260
GE (clinical)	GE (confirmed) plus		
	D73	Gastroenteritis presumed infection	2307
	D11	Diarrhoea	2267
GE (symptomatic)	GE (clinical) plus		
	D09	Nausea	1237
	D10	Vomiting	439
GE (broad)	GE (symptomatic) plus		
	D06	Abdominal pain localized other	7798
	D08	Flatulence/gas/belching	277
IBS	D93	Irritable bowel syndrome	2358

* Patients may have had multiple different ICPC codes so numbers are not additive. For IBS, number of events presented are during entire follow-up period (1998–2010).

The unadjusted RR of developing IBS after GE was estimated at 6 months, 9 months, 1 year, 2 years, 3 years, 4 years, 5 years and at any time point. The RR at 1 year was also estimated using negative binomial regression to adjust for age, gender, time of visit, and practice. For sparse data with zero cells, the RR and 95% confidence intervals (CIs) were estimated by adding 0·5 to each cell and using standard equations. Risk factors and comorbidities for IBS in GE patients were tested using univariate and multivariate logistic regression (backwards elimination). Due to the large number of comparisons and the potential for spurious results, risk factors and comorbidities were only considered significant if 95% CIs from both the univariate and multivariate analyses did not contain 1 and the *P* value from the multivariate analysis was $<0{\cdot}02$. Survival analysis techniques were used to analyse time to IBS diagnosis and confirm risk factors. The impact of medical registration system was assessed by repeating the analysis separately for each system (not shown). Statistical analyses were performed using SAS v. 9.2 for Windows (SAS Institute Inc., USA).

RESULTS

Sample characteristics

Between 1998 and 2009, there were 728 937 patient-years of follow-up in the PCNU database and 2464 patients diagnosed with GE. A matched sample of 2462 patients consulting with non-GE symptoms was drawn for the reference group (Fig. 1).

Demographic characteristics, healthcare-seeking behaviours and comorbidities are presented in the online Supplementary Tables. About half of GE patients were female with an average age of 37·85 years. The distribution of socioeconomic status was similar across groups ($P=0{\cdot}9901$). GE and non-GE patients visited their primary-care physician a mean of 6·2 and 2·39 times per year, respectively, throughout the study period ($P<0{\cdot}0001$). Only 9% of non-GE patients consulted $\geqslant 5$ times annually during the study period compared to 39% of GE patients ($P<0{\cdot}0001$).

Most (84·6%) GE patients had only one exposure to GE during the study period. Similar proportions of GE and non-GE patients had concomitant diagnoses of bloody stools (0·4% *vs.* 0·0%, $P=0{\cdot}0114$), weight loss (0·0% *vs.* 0·0%, $P=0{\cdot}9995$) and history of ulcer (0·1% *vs.* 0·0%, $P=0{\cdot}5641$). Higher proportions of GE patients had concomitant abdominal cramps (1·4% *vs.* 0·1%, $P<0{\cdot}0001$) and symptoms of dyspepsia (3·4% *vs.* 0·8%, $P<0{\cdot}0001$) compared to non-GE patients. GE patients were also more likely than non-GE patients to have a history of psychological problems (10·3% *vs.* 5·2%, $P<0{\cdot}0001$), social problems (3·3% *vs.* 2·0%, $P<0{\cdot}0001$), fear of disease (3·1% *vs.* 2·6%, $P=0{\cdot}2688$) and unexplained symptoms (5·0% *vs.* 3·5%, $P=0{\cdot}0109$).

Outcomes of interest

Between 1998 and 2010, there were 2358 consultations in the PCNU for IBS. Over half of IBS cases were between the ages of 18 and 40 years. Most (75%) were female. Four PCNU practices reported similar consultation rates for IBS (range 18–22%) while the remaining two practices reported much lower

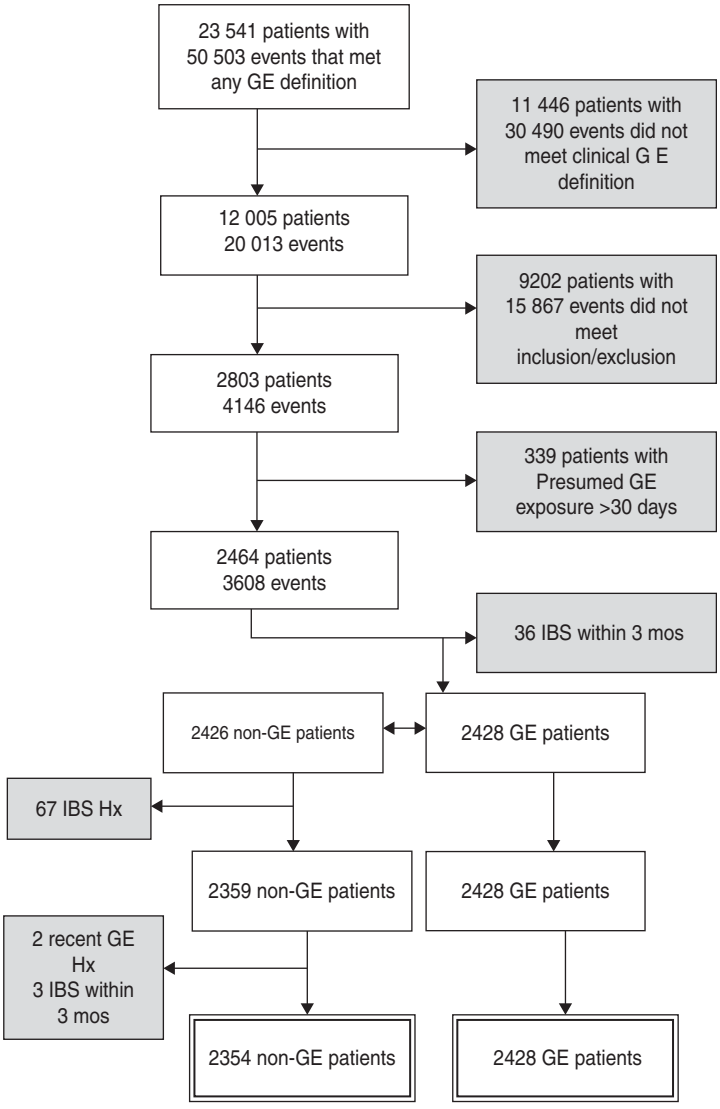

Fig. 1. Summary of patients with gastroenteritis (GE) exposure during the study period.

consultation rates (range 9–12%). Over half of IBS cases seen in the PCNU during the study period had a mean consultation frequency of more than four consultations per year.

Of the 2464 GE patients, 36 developed IBS within 3 months of their study exposure and, along with their reference patients, were excluded from the analysis. Of the 2462 matched non-GE patients, 72 were excluded due to prior history of IBS ($n=67$), prior history of GE ($n=2$) and developing IBS within 3 months of study entry ($n=3$). Therefore, 2428 GE patients and 2354 non-GE patients were included in the analysis.

During the study period, 4·9% of included GE patients were diagnosed with IBS compared to 0·9% of non-GE patients. At 1 year post-exposure, the incidence of IBS in GE patients was 1·2/1000 person-years compared to 0·3 in non-GE patients. At 1 year, the adjusted RR of IBS following GE was 4·85 (95% CI 2·02–11·63) (Table 2). At 5 years post-exposure, the cumulative adjusted RR of IBS was still significantly higher in GE patients than in non-GE patients (RR 5·40, 95% CI 2·60–11·24) (Fig. 2). With the exception of confirmed GE cases, this increased risk was consistent across GE definitions and time points (see online Supplementary Table S4). For confirmed GE cases ($N=137$), there was an increased risk at any time point in the study but not at individual time points.

Time to event

The median time to IBS was lower in GE patients (555·5 days) than in non-GE patients (863·5).

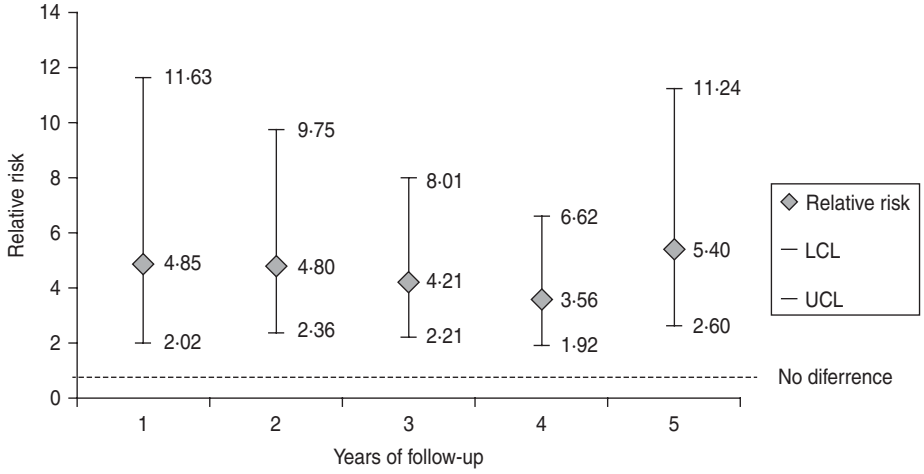

Fig. 2. Relative risk of irritable bowel syndrome following gastroenteritis. Bars indicate upper (UCL) and lower (LCL) 95% confidence intervals.

Table 2. *Relative risk (RR) and 95% confidence interval (CI) of irritable bowel syndrome at 12 months*

Gastroenteritis	
Confirmed	0/130 controls (0%) 3/134 cases (2·3%) RR 6·79 (95% CI 0·35–130·23)
Clinical	6/2354 controls (0·3%) 30/2428 cases (1·2%) **RR 4·85 (95% CI 2·02–11·63)**
Symptomatic	7/2978 controls (0·2%) 43/3088 cases (1·4%) **RR 5·92 (95% CI 2·67–13·15)**
Broad	17/5877 controls (0·3%) 99/6071 cases (1·6%) **RR 5·64 (95% CI 3·37–9·42)**

Significant results appear in bold.

Differences were also seen in the minimum time to IBS (99 days *vs.* 144 days). The maximum time to IBS was similar between GE (3367 days) and non-GE (3609 days) patients.

Risk factors

Odds ratios, 95% CIs and *P* values for significant risk factors 1 year post-GE are presented in Table 3. In the univariate analysis, consultation frequency, multiple GE exposures, concomitant cramps, dyspepsia history, psychosocial history and history of fear consultations before study entry were significant. In the multivariate analysis, concomitant cramps and psycho-social history were significant. At any time point, visit year, practice, consultation frequency and concomitant cramps were found to be significant risk factors for IBS in both the univariate and multivariate analyses (results not shown). In the univariate survival analysis, GE exposure, female gender, socio-economic status, age group, consultation frequency, concomitant cramps, weight loss, dyspepsia history, psycho-social history, social consultations and multiple GE exposures were significant risk factors (Fig. 3*a–f*). In the multivariate analysis, female gender, age group, consultation frequency, concomitant cramps, weight loss and psycho-social history were significant risk factors.

DISCUSSION

Foodborne illness is a significant public health issue that can cause significant morbidity and mortality. Several studies have found an increased risk of IBS following acute episodes of foodborne disease but few have examined the risk of IBS prospectively. In the present study using primary-care electronic medical records over a 12-year observational period, we found a fivefold increased risk of IBS after a gastrointestinal infection.

A 2006 meta-analysis of six cohort studies found the median prevalence of IBS in GE patients to be 9·8% (95% CI 4·0–13·3) [1]. A subsequent meta-analysis of 18 cohort studies found a 10% (95% CI 9·4–85·6) pooled incidence of IBS following GE [2]. A UK study using a general practice research database found the incidence of IBS after GE to be 10/1000 person-years [22]. The incidence in the present study is significantly lower than either meta-analysis

Table 3. *Risk factors for IBS at 12 months*

	Logistic regression			Survival analysis	
Risk factor	Univariate OR (95% CI)	Multivariate OR (95% CI)	Multivariate *P* value	Univariate *P* value	Multivariate *P* value
Age group	0·85 (0·65–1·11)	0·79 (0·59–1·05)	0·0988	**0·0127**	**<0·0001**
Female gender	n.s.	n.s.	n.s.	**<0·0001**	0·0405
Socioeconomic status	n.s.	n.s.	n.s.	0·0220	n.s.
Practice	1·17 (0·98–1·40)	1·18 (0·98–1·42)	0·0871	n.s.	n.s.
Consultation frequency	**1·68 (1·02–2·79)**	1·61 (0·93–2·79)	0·0920	**<0·0001**	**0·0018**
Multiple gastroenteritis	**2·73 (1·27–5·88)**	**2·49 (1·13–5·50)**	0·0236	**<0·0001**	n.s.
Concomitant cramps	**12·57 (4·12–38·31)**	**13·55 (4·20–43·73)**	**0·000**	**<0·0001**	**0·0160**
Weight loss	n.s.	n.s.	n.s.	**0·0005**	0·0433
Dyspepsia history	**6·11 (2·28–16·40)**	n.s.	n.s.	**0·0033**	n.s.
Psycho-social history	**3·85 (1·75–8·51)**	**3·60 (1·56–8·29)**	**0·0026**	**<0·0001**	**0·0140**
Fear history	**3·54 (1·05–11·93)**	n.s.	n.s.	n.s.	n.s.

OR, Odds ratio; CI, confidence interval; n.s., risk factor was not significant and not included in the final model. Significant results (ORs and 95% CIs that do not contain 1 and *P* values <0·02) appear in bold.

or the UK study, which may be a function of the PCNU database. The lower incidence of IBS may also reflect the passive design of a study that employs an existing electronic database of routine care registration data.

We found an increased risk of IBS at 1 year following GE. In our study, GE patients were 4·85 (95% CI 2·02–11·63) times more likely to develop IBS than the reference group. In the UK study, which used Oxford Medical Indexing System and Read diagnostic codes, the RR of IBS following bacterial GE was 2·2 (95% CI 1·5–2·9) [22]. However, an earlier study using the same database found the adjusted RR of IBS to be 11·9 (95% CI 6·7–21·0) [18]. Recent meta-analyses of prospective studies found pooled odds ratios of 7·3 (95% CI 4·7–11·1) and 6·37 (95% CI 2·63–15·40), respectively, for IBS at 1 year. These estimates are higher than our findings which may be due to differences in exposure and outcome definitions. In the present study, we defined incident cases of IBS to be those with an ICPC diagnostic code for IBS and no prior history of IBS. Many other studies have used a stricter outcome definition, requiring multiple visits for IBS in conjunction with medical treatment. Due to our less stringent definition, it is possible that some patients were misclassified as IBS in this study when they may not have met more traditional definitions. However, since the CIs in the present study overlap with those from the meta-analyses, it is not possible to determine if the point estimates are significantly different.

Several studies have examined risk factors for PI-IBS [21, 28–34]. As found previously, risk of IBS was higher in females and younger age groups, although this was not significant. Individuals with higher levels of socioeconomic status were less likely to develop IBS at 1 year. The demographic characteristics of the PCNU practices may have contributed to these findings. Many PCNU practices are located in newly developed areas, which could skew the patient population towards younger families with higher socioeconomic status. However, this does not fully account for the increased risk.

It has been hypothesized that GE exposure may trigger an inflammatory response and contribute to hypersensitivity [8, 26]. More severe and/or repeated exposures may increase or prolong inflammatory response and are considered to be potential risk factors for IBS [8, 28, 30, 31, 34]. Our finding of increased risk of IBS in GE patients with concomitant abdominal cramps is consistent with other studies [31]. Interestingly, bloody diarrhoea, a marker of severe disease, was not a significant risk factor. Weight loss was also not found to be significant, although the guidelines for coding of weight loss in the PCNU are unclear and, as a consequence, weight loss may only be reported in severe cases. As in previous studies, we found an increased risk of IBS in GE patients with a history of dyspepsia [22]. We also found an increased risk of IBS in GE patients with multiple GE exposures, although it is possible that these were undiagnosed cases of IBS.

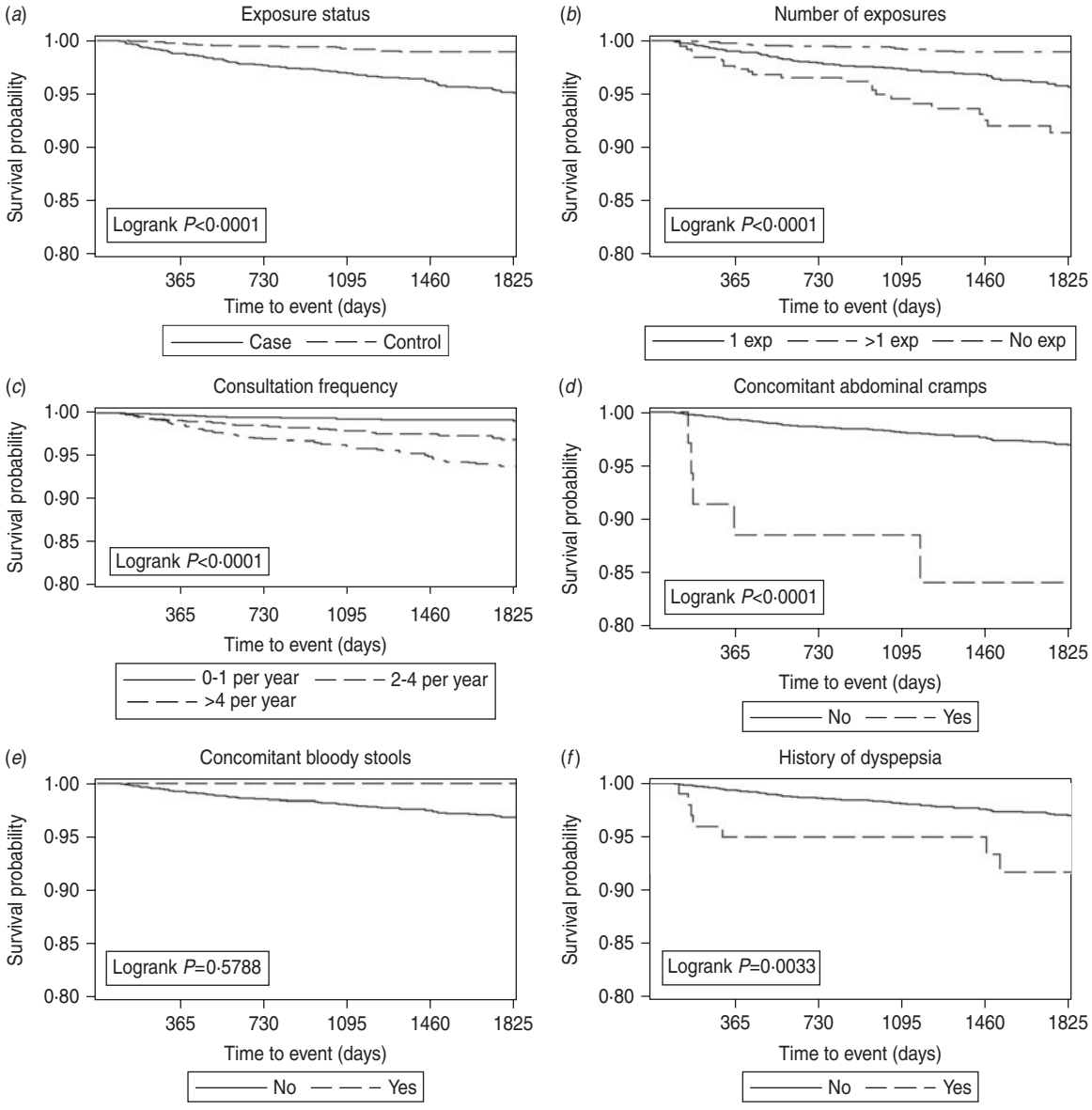

Fig. 3. Survival function of irritable bowel syndrome following gastroenteritis by (*a*) exposure status, (*b*) number of exposures, (*c*) consultation frequency, (*d*) concomitant abdominal cramps, (*e*) concomitant bloody diarrhoea, (*f*) history of dyspepsia.

Overall, these findings support the hypothesis that severity of exposure and/or prolonged exposure increases risk of IBS.

Previous studies have hypothesized that psychological stress may increase or sustain inflammatory response to infection and increase the risk of IBS [22, 26, 28, 32, 35–37]. To evaluate this, we used a prior history of consultation (within 1 year) for psychological and social problems as a proxy indicator for presence of psychological stress. History of psycho-social consultations was a significant predictor for IBS at 12 months.

Healthcare-seeking behaviours have also been associated with increased risk [15, 16, 33, 38]. The hypothesis is that some patients seek help for even minor symptoms and, since IBS is often a diagnosis of elimination rather than confirmation, are more likely to be diagnosed. We used several surrogate markers, including consultation frequency, history of unexplained symptoms and history of fear of disease, to evaluate healthcare-seeking behaviors. Consultation frequency was generally higher in GE patients and was a significant risk factor in the univariate analysis. Since we examined consultation frequency

across the study period, it is not possible to determine if consultation frequency was consistent over time or changed with exposure. History of fear of disease consultations was also a significant risk factor in the univariate logistic regression analysis. This may indicate a pattern of seeking help for even minor symptoms or an underlying psychological issue. However, it could also suggest a medical condition with no structural cause, such as IBS. The nature of the association of consultation frequency and history of fear of disease with increased risk of IBS should be explored in a larger prospective study.

Although the primary endpoint was 1 year, we also examined the risk of IBS at 6 months, 9 months, 1 year, 2 years, 3 years, 4 years and 5 years. The hazard function associated with IBS for GE and non-GE patients was also estimated using survival analysis. We found that GE patients had a higher risk of IBS than non-GE patients up to 5 years post-exposure. These findings are curious, as we anticipated an increased risk up to 2 years post-GE that would then level off and trend towards the prevalence of sporadic IBS. The increased risk in GE patients up to 5 years post-GE could be the result of uncontrolled confounders or diagnostic delays. First, patients with GE may suffer from an underlying susceptibility to both GE and IBS. A prospective cohort study of GE patients in Canada found that single nucleotide polymorphisms in genes that encode proteins involved in epithelial cell barrier function and innate immune response were significant risk factors for developing PI-IBS [39]. A Dutch case-control study found that host genetic factors played a role in susceptibility to reactive arthritis and recurrent GE episodes after severe *Salmonella* and *Campylobacter* infections [40]. Due to a lack of genetic samples, we were unable to explore the role of host genetics in susceptibility. Second, GE exposure may have changed intestinal microflora, putting exposed patients at increased risk of IBS and GE over time. Finally, physicians may be reluctant to diagnose IBS and may only do so if problems persist over time. Therefore, patients in our study may have had a delayed diagnosis of IBS. The increased risk at 5 years could have also been the result of multiple GE exposures or pathoaetiology of the GE infection. However, since many GE exposures were not laboratory confirmed, it is not possible to determine if this influenced the results. Additional research is needed to understand factors that influence long-term risk of IBS in patients exposed to GE.

There are several study limitations. First, GE patients may not be representative of all patients with GE since many do not seek medical care. Second, healthcare-seeking behaviours may have influenced the results. Since GE consultation may be related to severity of illness, the incidence of GE may be underestimated and the risk of IBS may be overestimated compared to a general population cohort [38]. In addition, patients with undiagnosed IBS may seek healthcare more often than non-IBS patients and, therefore, may be more likely to be diagnosed with GE. This would overestimate the risk of IBS following GE. Third, there is potential for misclassification biases. The GE definitions used in the present study include potential IBS symptoms and patients with GE exposure may actually have undiagnosed IBS. Further, there is substantial overlap between upper and lower GI symptoms, such as dyspepsia and IBS, which may be reflected in the diagnostic codes. To address these potential misclassification biases, we evaluated multiple GE definitions and excluded patients with GE symptoms in the previous 12 months and patients diagnosed with IBS within 3 months of study entry. Increased risk for IBS was found across GE definitions and time points, suggesting that these results are not affected by GE definition. Criteria used to diagnose IBS can lead to different classifications of patients [1, 4, 6]. However, due to a lack of standards and documentation regarding IBS diagnosis in the PCNU, we could not assess the impact of diagnostic criteria on the study results. Further, in 2006, when three PCNU practices switched to a registration system that required a diagnostic code, the incidence of both GE and IBS increased significantly, suggesting that GPs may be reluctant to formally diagnose GE and IBS otherwise. Stratified analyses were undertaken to further assess the impact of the registration system. The majority of patients were registered before 2006 using a single registration system. Post-2006, a small number of patients (<500 per group) were registered under two new systems, resulting in insufficient power to detect a difference. The impact of registration system on the incidence of diagnostic codes for GE and IBS do, however, raise interesting implications for the use of electronic medical records to evaluate outcomes and should be explored. A lack of data on pre-morbid bowel habits prevented us from identifying patients with undiagnosed IBS. Stool studies to verify the cause of GE in cases and absence of gastrointestinal pathogens in controls were unavailable. Fourth, limited electronic information

also precluded inclusion of risk factors found to be significant in previous studies. For example, duration of diarrhoea and smoking have been previously associated with increased risk of PI-IBS [8, 28, 29, 31, 34]; however, this information was not recorded in the PCNU database and could not be considered in this study. Finally, we were unable to assess the impact of disruptions in the intestinal microflora, comorbidities and genetic susceptibility on the results.

CONCLUSION

IBS is a significant public health issue that is associated with GE. Patients were at increased risk of IBS 1 year post-exposure compared to unexposed patients and remained so up to 5 years post-exposure, suggesting that not only GE but also other factors may play a role. Concomitant cramps and psycho-social consultations were found to be significant risk factors. Prospective studies are needed to assess the impact of these factors on the development of IBS following GE. Additional research is also needed to understand the biological basis of IBS following GE and clarify causality.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268813001891.

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DECLARATION OF INTEREST

None.

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