Determining the Risk of Depressive Disorder as a Sequela of a Foodborne Infection Using Administrative Data from British Columbia, Canada: A Retrospective Population-Based Cohort Study

Valerie Rodrigue

Department of Epidemiology, Biostatistics, and Occupational Health
McGill University, Montreal
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ABSTRACT

Background: An increasing number of studies demonstrate that depressive disorders (DD) can be a sequela of infection. Despite the growing attention directed to the gut-brain axis, few studies have explored the role of foodborne illnesses (FBIs) in developing DD and none evaluate the long-term impact of identified pathogens. Studies with a longer follow-up time and laboratory-confirmed identification of the pathogens involved are needed to assess the individual impact of different foodborne pathogens on the risk of developing DD.

Objective: The aim of this study was to determine whether exposure to fourteen FBIs of interest (botulism, Campylobacter, Cryptosporidium, Cyclospora, Giardia, Hepatitis A, Listeria, Salmonella spp. (non-typhoidal, Typhi, Paratyphi), Shiga Toxin–Producing Escherichia Coli (STEC), Shigella, Vibrio parahaemolyticus, and Yersinia) increases the risk of DD.

Methods: For this manuscript-based thesis, I conducted a retrospective cohort study of all residents of British Columbia living in the province between Jan. 1, 2005 to Dec. 31, 2014 (approximately 4.7 million). All laboratory confirmed FBIs captured in the province's surveillance system, Panorama, were linked with six administrative health data sets including PharmaNet, BC's comprehensive database of all prescription drug fills irrespective of payer. I used 4:1 matching and Cox proportional hazard models to estimate the hazard ratios and corresponding 95% confidence intervals of DD incidence following exposure to each of the 14 FBIs, comparing individuals exposed to one FBI during the study period with those unexposed. Adjusted hazard ratios were calculated to account for the impact of covariates including age, sex, income decile, local health area, comorbidities and exposure to antibiotics, proton-pump inhibitors, statins, and immunosuppressive and immunomodulatory agents.

Results: A total of 33,360 exposed patients and 133,068 unexposed patients, matched on sex, exact age, and length of MSP coverage were included in this study. During a mean follow-up period of 5.80 years, 4,515 (23.7 per 1000 person-years) incident cases of DD were detected in the exposed patients and 12,273 (15.8 per 1000 person-years) in the unexposed patients. Patients with laboratory-confirmed exposure to an FBI were 38% more likely to develop DD (adjusted hazard ratio (HR) 1.38, 95% confidence interval (CI) 1.33-1.43) than patients who had not been exposed.

Recent exposure to antibiotics, a known risk factor for developing DD, was more prevalent in the exposed group than in the unexposed (8.9% vs 3.2%). After stratifying the data on exposure to antibiotics, the HR remains statistically significant (adj.HR 1.14, 95%CI 1.01-1.28). Sex and Irritable Bowel Syndrome (IBS) status were not found to be statistically significant effect modifiers. In individual pathogens analysis, campylobacter (adj.HR 1.36, 95%CI 1.28-1.44), non-typhoidal salmonella (adj.HR 1.40, 95%CI 1.29-1.52), giardia (adj.HR 1.34, 95%CI 1.21-1.48), yersinia (adj.HR 1.58, 95%CI 1.44-1.74) and shigella (adj.HR 1.55, 95%CI 1.30-1.85) were all associated with an increased risk of DD. STEC was not associated with a higher risk of developing DD (HR 1.15, 95% CI 0.93-1.42).

Discussion: Exposure to FBIs is associated with a higher risk of developing DD. Yersiniosis is associated with a greater risk of developing DD than other FBIs, possibly because the greater prevalence of chronic gastro-intestinal (GI) conditions in yersinia patients. Those finding are in line with those of prior studies linking GI infections with a higher risk of developing mood disorders, although the link described in the literature between STEC and DD was not observed in this study.

Conclusion: Given its association with subsequent development of DD, laboratory-confirmed exposure to FBIs could serve as an indicator for clinicians that a more proactive approach for prevention and early detection of DD is needed in exposed patients.

RÉSUMÉ

Contexte: Plusieurs études ont indiqué que les troubles dépressifs (TD) peuvent être une séquelle d'une infection. Malgré l'intérêt croissant envers l'axe intestin-cerveau, peu d'études ont exploré le rôle des Infections d'Origine Alimentaire (IOA) dans le développement des TD et aucune n'a évalué l'impact à long terme de pathogènes spécifiques. Des études suivant sur une longue période des patients dont le pathogène a été identifié en laboratoire sont requises pour évaluer l'impact de différentes IOA sur le risque de TD.

Objectif: L'objectif de cette thèse était de déterminer si l'exposition à 14 IOA (botulisme, Campylobacter, Cryptosporidium, Cyclospora, Giardia, Hépatite A, Listéria, Salmonella spp. (non-typhoïde, Typhi, Paratyphi), Escherichia Coli producteurs de Shigatoxines (STEC), Shigella, Vibrio parahaemolyticus, et Yersinia) augmente le risque de développer un TD.

Méthodes: J'ai conduit une étude de cohorte rétrospective de tous les résidents de Colombie-Britannique (CB) vivant dans la province entre le 1er janv. 2005 et le 31 déc. 2014 (env. 4.7 millions). Les cas d'IOA confirmés par laboratoire et capturés dans la base de surveillance Panorama, ont été liés avec les données de six bases administratives incluant PharmaNet, qui contient toutes les prescriptions servies en CB, sans égard au payeur. Les modèles de risques proportionnels de Cox ont été utilisés avec un appariement cas:témoins de 1:4 pour calculer les rapports de risque (RR) de l'incidence des TD ainsi que les intervalles de confiance (IC) à 95% suivant l'exposition aux 14 IOA, comparant les individus exposés à une IOA et les individus non-exposés. Les RR ont été ajustés en fonction de l'âge, le sexe, le décile de revenu, la sous-région sanitaire, les comorbidités et l'exposition aux antibiotiques, inhibiteurs de la pompe à protons, statines ainsi qu'agents immunosuppresseurs et immunomodulateurs.

Résultats: 33 360 patients exposés et 133 068 patients non-exposés, appariés sur le sexe, l'âge exact et la durée de la couverture MSP ont été inclus dans cette étude. Sur un suivi moyen de 5.80 ans, 4 515 (23.7 pour 1000 pers.-années) cas incidents de TD ont été détectés chez les patients exposés et 12 273 (15.8 pour 1000 pers.-années) chez les patients non-exposés. Les patients exposés avaient 38% plus de risques de développer un TD (RR aj. 1.38 IC 95% 1.33-1.43) que les patients non-exposés. L'usage récent d'antibiotiques, un facteur de risque de TD, était plus

commun dans le groupe exposé à une IOA que dans le groupe non-exposé (8.9% vs 3.2%). Après stratification en fonction de l'usage d'antibiotiques, le RR demeure significatif (RR aj. 1.14, IC95% 1.01-1.28). Le sexe et la présence d'un diagnostic de syndrome de l'intestin irritable ne sont pas des modificateurs d'effet significatifs. Lors des analyses individuelles, les pathogènes campylobacter (RR aj 1.36, IC95% 1.28-1.44), salmonella non-typhoïde (RR aj 1.40, IC95% 1.29-1.52), giardia (RR aj 1.34, IC95% 1.21-1.48), yersinia (RR aj 1.58, IC95% 1.44-1.74) and shigella (RR aj 1.55, IC95% 1.30-1.85) ont tous été associés à une hausse du risque de TD. Le pathogène STEC n'a pas été associé à un risque accru de TD (RR aj 1.15, IC95% 0.93-1.42).

Discussion: Une association a été démontrée entre les IOA et le risque de TD. La bactérie yersinia est associée à un risque accru de TD par rapport aux autres pathogènes, possiblement dû à la prévalence plus élevée de conditions gastro-intestinales (GI) chez les patients atteints de yersiniose. Ces résultats sont alignés avec ceux des autres études, qui indiquent un lien entre les infections GI et le risque de troubles affectifs, bien que le lien entre le STEC et les TD décrit dans une autre étude n'a pas été observé dans cette étude.

Conclusion: Au vu de son association avec les TD, la confirmation par laboratoire d'une IOA pourrait être un indicateur pour les cliniciens qu'une approche plus proactive de prévention et de détection des TD est appropriée.

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CONTRIBUTION OF AUTHORS

Valerie Rodrigue developed the research question, performed the statistical analyses and drafted the thesis and the manuscript with guidance from her supervisor, Dr. Dimitra Panagiotoglou. Dr. Erica Moodie provided expertise on propensity score calculation as well as statistical methods and helped adjust the initial methodology. Dr. Dimitra Panagiotoglou and Dr. Eleni Galanis contributed to the interpretation of the results obtained. Dr. Dimitra Panagiotoglou, Dr. Erica Moodie, Dr. Eleni Galanis and Marsha Taylor reviewed the manuscript and suggested edits based on their respective expertise. Dr. Shannon Majowicz acquired the data used for the project. Esther Lin (pharmacist) reviewed the list of drugs to be considered in the analysis to exclude those with no plausible systemic effect.

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ABBREVIATIONS

AHFS:	American Hospital Formulary Service
BC:	British Columbia
BCCDC:	British Columbia Center for Disease Control
CCI:	Charlson comorbidity index
CI:	Confidence interval
DAD:	Discharge abstract database
DD:	Depressive disorders
DIN:	Drug identification number
FBI:	Foodborne Illness
GI:	Gastro-intestinal
HR:	Hazard ratio
IBS:	Irritable bowel syndrome
ICD:	International classification of diseases
IRR:	Incidence rate ratio
LHA:	Local health authority
MDD:	Major depressive disorder
MSP:	Medical service file
PPI:	Proton-pump inhibitor
RCT	Randomized Controlled Trial
STEC:	Shiga Toxin–Producing Escherichia Coli
VS:	Vital events and statistics: Deaths

1. STATEMENT OF RESEARCH PROBLEM

Depressive Disorders (DD), also known as affective disorders or, more colloquially, depression, are a group of mental health disorders characterised by depressed/irritable mood and by the impairment of daily functioning due to somatic and cognitive changes [1]. In the province of British Columbia, about 50,000 incident cases of DD are recorded each year, with a prevalence of 7.34 cases per 100 population in 2017, which translates to more than one person out of 14 suffering from DD at any given time [2].

DD carry many negative consequences, both on an individual and collective level. In a longitudinal study of Canadian workers, employed individuals aged 26-45 who were experiencing a major depressive episode were 2.6 time more likely to be unemployed two years later compared with non-depressed workers [3]. Analysis of the data collected through the Canadian National Population Health Survey (NPHS) also demonstrated that individuals with DD at the baseline interview were more likely to report a new diagnosis of a chronic conditions in the eight years following the initial assessment, including hypertension, back problems and respiratory problems [4]. In Canada, loss of worker productivity due to depression has been estimated to cost the economy $32.3 billions in foregone gross domestic product [5]. On a global scale, Major Depressive Disorder (MDD), the main condition of the DD group, was the fifth cause that generated the most years lived with disability in the 195 countries and territories included in the Global Burden of Diseases, Injuries and Risk Factors Study in 2016 [6].

Past research has shown that Irritable Bowel Syndrome (IBS) is associated with a higher likelihood of exhibiting depressive symptoms [7]. Patients with a history of non-specific gastrointestinal (GI) infections have also been found to be more likely to be subsequently diagnosed with mood disorders, especially if they have had a pre-existing diagnosis of IBS or another autoimmune disease [8]. A German study found infection by Shiga Toxin–Producing Escherichia Coli O104 (STEC) to be associated with a higher risk of meeting the criteria for MDD 6 months after the

initial onset of the FBI, despite the physical component of the patients' health-related quality of life score being back to a value comparable to that of the general population [9].

However, despite the substantial incidence and widespread economic and social impact of DD [3-6] as well as the existence of some literature suggesting an association between foodborne illnesses (FBIs) and DD [8-10], the role of individual foodborne pathogens in the development of DD has not been explored. Existing studies either do not have laboratory-confirmed identification of the pathogen(s) involved or follow patient mental health for only a few months post FBI. A large study with laboratory-confirmed identification of pathogens, assessing the distinct impact of the most frequent foodborne pathogens on the mental heath of patients and following up patients for multiple years after the infection has yet to be conducted. The combined effect of FBIs and IBS on the likelihood of developing DD is also unknown.

Because of this lack of quantified evidence about the possible association between FBIs and DD, clinicians are mostly unaware of this possible link and are left ill-equipped to take measures to prevent, evaluate and remediate the development of depressive symptoms in their patients with FBIs. Further, since FBIs are an exposure that is modifiable, significant findings could help justify the development of better food handling policies and of nutritional recommendations for individuals at high risk of developing DD.

The aim of this study is to determine whether exposure to FBIs increase the risk of a post-FBI new diagnosis of DD and whether this exposure has the same impact on individuals who have IBS as a comorbidity.

2. BACKGROUND

2.1 Depressive Disorders

The diverse conditions in the DD group differ from each other by duration and severity of the symptoms as well as main causal factor [1]. Patients suffering from MDD, the main condition of the group, usually present with a subset of the following nine symptoms: depressed/irritable mood, loss of interest in most activities, changes in appetite, changes in sleeping patterns, fatigue, psychomotor agitation or retardation, decreased concentration, feelings of worthlessness and/or guilt, recurrent thoughts of death and/or suicidal ideation [1]. For a diagnosis of MDD to be made, a patient must present with at least five of these symptoms for a period of at least 2 weeks, and one of the symptoms must be either depressed/irritable mood or loss of interest in most activities [1]. Moreover, the symptoms must negatively impact the everyday life of the patient and must not be plausibly caused by another medical condition [1]. Depending on the evolution of the symptoms, patients might experience a single depressive episode, recurrent depressive episodes or chronic depressive disorder in the course of their lifetime. In the case of chronic depressive disorder, in the two years following the onset of the symptoms, the patient never experiences a period of at least two months without symptoms [1]. Other disorders of the group have similar symptoms, but are usually linked to specific circumstances, such as substance-induced depressive disorder and premenstrual dysphoric disorder [1].

2.1.1 Burden of Disease

DD have been associated with a significantly lower healthy life expectancy, both due to premature mortality and reduced health-related quality of life [11]. In a Canadian study, the health-adjusted life expectancy at age 20 was reduced by 15 years in depressed women and by 14,8 years in depressed men, compared to non-depressed individuals of the same sex [11]. Depression has also been associated with a decreased likelihood of being employed and an increased likelihood of developing chronic conditions in the years following the depression diagnosis [3, 4].

2.1.2 Etiology

Social, psychological, genetic and biological factors are associated with the development of an episode of DD [12-14]. Therefore, the factors that trigger DD differ across patients [12]. Sociodemographic factors that have been associated with DD include age, low educational achievement, low income level, living in an urban area, being female, being non-white and being unmarried [14].

2.1.2.1 Psychological and Social Factors

Stressful life events as well as the perception an individual has of these events and of the resources available to face them influence the likelihood of developing DD [13, 15]. Perceiving a stressful life event as negative has been associated with a threefold increase in the likelihood of MDD in the following year, while perceiving an event as uncontrollable has been associated with an almost sevenfold increase in the likelihood of MDD [15].

Unsurprisingly, the presence of social support has been linked by numerous studies to a reduction of the likelihood of an individual developing DD [16]. A recent meta-analysis found that perceived social support, whether from family, friends or larger social circle, is associated with a 47% decrease in the odds of DD [16].

The personality traits of an individual might also influence likelihood of developing DD [17, 18]. A Finnish study found that depressed subjects were markedly more likely than the general population to exhibit a high neuroticism score on the Eysenck personality inventory and also more likely to exhibit a low extraversion score [18].

2.1.2.2 Biological Factors

The biological triggers of depression are still widely misunderstood. Since multiple event sequences, interacting neurotransmitters and brain structures are involved, it is difficult to distinguish the causal event of a chain reaction [19].

Depression can be characterised by chemical imbalances in the brain's neurotransmitters, such as serotonin, norepinephrine and dopamine [14]. A modification in the circulation of these

neurotransmitters, whether due to obstacles in their regular emission, transportation, or reuptake patterns is often observed in depressed individuals [14].

DD have also been linked with inflammation and are frequently associated with inflammatory comorbid conditions, such as IBS, arthritis, diabetes and obesity [7, 20]. It has been postulated that this association might be caused by the similar inflammatory mechanisms that are involved in the etiology of both DD and inflammatory disorders [20, 21]. For example, elevated concentrations of many biomarkers that are involved in inflammatory processes, such as pro-inflammatory cytokines and kynurenine metabolites have been found in depressed individuals [20].

Numerous studies have also uncovered differences in the size of various brain structures in depressed patients compared with non-depressed patients. In particular the hippocampus has been found to be smaller in depressed individuals, while the amygdala can be larger and shows altered connectivity between its different subregions [19, 22]

2.1.2.3 Genetic Factors

Multiple genes have been linked to a higher likelihood of developing DD through different action mechanisms [13]. Some genetic variants impact the emission, transmission or reuptake of neurotransmitters that have an influence on mood, such as the 5-HTTLPR short variant of the serotonin transporter-linked polymorphic region [13]. Pro-inflammatory variants of immune genes have also been linked with the development of DD [13]. Due to the numbing effect of endogenous opioids, genes that impact opioid production by the body might also have an influence in the likelihood of developing DD [13].

2.2 Foodborne Infections

While some foodborne pathogens can also be acquired through contaminated drinking or recreational water or through contact with a contaminated person, animal or surface, foodborne infections are known as such because they are mainly transmitted through eating contaminated food products [23]. Animal products (meat, eggs, dairy) are a well known vehicle for foodborne pathogens, but they can also originate from other types of food, such as vegetables, grains and nuts, which may be contaminated through exposure to manure, contaminated irrigation water, water runoffs from surrounding pasturages or contaminated food handlers, among other sources [23].

Despite the development of more stringent food handling policies in industrialized countries, the risk of exposure to an FBI remains substantial, fuelled up by factors such as the globalization of food chains, which makes the tracing of ingredients and contamination sources difficult. Intensive and large-scale animal production, which increase the risk of animals being infected by foodborne pathogens and the increased popularity of microwaving, which does not develop enough heat to kill pathogens that would be eliminated by oven/skillet cooking are also contributing to this risk [23].

Of the 14 pathogens examined in this thesis, one is a virus (hepatitis A), three are parasites and ten are bacteria. Eight of the ten bacteria are defined as Gram-Negative, a designation related to the reaction of those bacteria to the process of Gram staining, and only two are Gram-Positive [24, 25]. The 14 pathogens were selected because they are all reportable in BC and are considered by the local health authorities to be a priority due to their health impacts and prevention potential [26]. Population most at risk is very similar for many of the pathogens, including young children, older adults and travellers [23, 27]. Incidence in 2017 in the province of British Columbia varied from 36.9 cases per 100,000 people for the most frequent pathogen, campylobacter, to 0.0 cases per 100,000 people for the rarest one, botulism [28]. Under-diagnosis is suspected for all pathogens included in the study, with estimated under-diagnosis multipliers ranging from 1.7 (Listeria) to 92.0 (Vibrio Parahemolyticus) [29]. Taking Vibrio Parahemolyticus as an example, a multiplier of 92.0 would mean we need to multiply the number of diagnosed cases by 92.0 to obtain the estimated total number of cases in the population [29]. Literature studying DD as a possible sequela of infection exist for only two of the individual pathogens, Giardia [30] and STEC [9].

Table 1 - Characteristics of the 14 foodborne pathogens under study

Pathogen name	Pathogen Type [25, 27]	Main Food Vector [27]	Population Most At Risk of Foodborne Transmission [27]	Incidence in BC in 2017 (per 100 000) [28]	Estimated Case Multiplier in Canada [29] *	Existing studies linking this pathogen to DD
Botulism (Clostridium Botulinum)	Bacterium (gram-positive)	Improperly canned or fermented foods, honey	People who eat home-canned or home-fermented foods	0,0	2,7	
Campylobacter	Bacterium (gram-negative)	Raw or undercooked poultry,	Males, Young children, Older Adults	36,9	27,2	
Cryptosporidium	parasite	Contaminated water (drinking or recreational)	Young Children, Older Adults, Travellers	1,8	48,5	
Cyclospora	parasite	Imported fresh produce, Contaminated water	Travellers, People living in tropical regions	1,2	53,5	
Giardia	parasite	Raw fruits and vegetables, Contaminated water	Travellers, People in childcare settings	11,6	40,7	X
Hepatitis A	virus	Food products contaminated by feces or blood of infected individuals	Travellers	0,3	13,9	
Listeria monocytogenes	Bacterium (gram-positive)	Deli meats, Dairy products, Fresh Produce	Pregnant women, Elderly Adults	0,2	1,7	
Salmonella (non-typhoidal)	Bacterium (gram-negative)	Beef and Poultry, Milk, Fish, Eggs	Infants, Young Children, Older adults,	22,4	26,1	

Pathogen name	Pathogen Type [25, 27]	Main Food Vector [27]	Population Most At Risk of Foodborne Transmission [27]	Incidence in BC in 2017 (per 100 000) [28]	Estimated Case Multiplier in Canada [29] *	Existing studies linking this pathogen to DD
Salmonella Paratyphi	Bacterium (gram-negative)	Food products contaminated by the feces of infected individuals	Travellers (especially to South Asian Countries)	0,4	N/A	
Salmonella Typhi	Bacterium (gram-negative)	Food products contaminated by the feces of infected individuals	Travellers (e specially to South Asian Countries)	0,8	12,7	
STEC	Bacterium (gram-negative)	Raw milk, Soft cheeses, Undercooked meat	Young Children, Older Adults	3,7	20,1	X
Shigella	Bacterium (gram-negative)	Food products contaminated by the feces of infected individuals	Young Children, Travellers	3,3	17,5	
Vibrio Parahemolyticus	Bacterium (gram-negative)	Raw or undercooked shellfish, particularly oysters	People with a weakened immune system or chronic liver disease	0,9	92,0	
Yersinia (excluding *pestis*)	Bacterium (gram-negative)	Raw or undercooked pork	Young Children	16,7	39,3	

***** The case multiplier accounts for both under-reporting of pathogens and under-diagnosis. The number of laboratory-confirmed cases reported in BC's provincial reportable disease database must be multiplied by this number to obtain the estimated total number of cases in the population.

2.3 Association Between Foodborne Illnesses and Major Depressive Disorder

2.3.1 Psychological impact of a Foodborne Illness

As previously explained, stressful life events might increase the risk of developing DD, especially in the case of events that are perceived by individuals to be negative or uncontrollable [15]. While the severity of FBIs varies widely by pathogen and from patient to patient, an FBI can be considered a stressful life event for a significant portion of patients. In a study of patients recovering from STEC 0104, almost half the participants (183/389) declared they had been afraid to die from the consequences of their infection [9]. In the study results, fear of death was associated with a higher score on the Patient Health Questionnaire (PHQ-9), a tool frequently used to diagnose depressive disorders [9]. Also, due to the incapacitating and sudden nature of FBIs, it is extremely likely that they will be perceived as a negative and uncontrollable event by patients, which would further increase the likelihood of developing DD.

2.3.2 Biological impact of Infection on the Brain

When the body is fighting an infection, the immune cells secrete molecules called cytokines, which concentrate at the site of the infection and in the blood. Pro-inflammatory cytokines are known to activate the nerve that connect the internal organs to the brain, the vagus nerve [31]. In turn, this activation of the vagus nerve by pro-inflammatory cytokines causes the production of cytokines directly in the brain, which is associated with the development of the "Sickness Behaviour", an adaptative response to disease that causes symptoms similar to those of depressive disorders, such as depressed mood, disturbed eating/sleeping pattern and lack of desire to socialize [32, 33]. Sickness behaviour is a normal component of the immune response and typically disappears when the infection recedes. However, in genetically, physically or psychologically predisposed patients, sickness behaviour might persist after an infection and transition to a DD [33]. Thus, an FBI-related secretion of pro-inflammatory cytokines by the immunes cells of the GI track could precipitate the development of DD in predisposed patients.

2.3.3 The Microbiota Dysbiosis Hypothesis

As the composition of the gut microbiota has been found to be significantly different in depressed and non-depressed individuals, the microbiota is hypothesized to have an impact on the mental

condition of patients through its influence on the gut-brain axis [34, 35]. Recent research also suggests that infection of the gut by a foodborne pathogen, such as Campylobacter and Giardia, might modify the microbiota composition for many months following an infection [36, 37]. It is thus possible that a durable modification of the microbiota induced by an FBI could influence the likelihood of a patient developing DD by creating a microbiota that stimulates the gut-brain axis in a way that favors depression.

The presence and abundance of certain species of bacteria in the gut also appear to have an influence on the risk of contracting an FBI. For example, an abundance of Dorea and Coprococcus bacteria in the gut has been associated with a lower risk of being infected with *Campylobacter Jejuni* [38]. As some sub-species of Coprococcus have been found to be less abundant in MDD patients [34], it is possible that some variations of the gut microbiota favor both infection by an FBI and development of DD in patients.

Antibiotics prescribed to cure an FBI might also cause microbiota dysbiosis[39]. In a Danish cohort, patients who had redeemed a prescription for antibiotics during the study period were found to be 64% more likely to be subsequently diagnosed with an affective disorder in a hospital setting [39]. The risk of being diagnosed with an affective disorder was highest in the 3 months following the redeeming of a prescription, decreasing with time. Patients who had received a broad spectrum antibiotic were at increased risk compared with those who had received narrow spectrum antibiotic [39]. As FBI patients might be prescribed antibiotics, the microbiota dysbiosis hypothesis predicts those patients could be more likely to suffer DD.

2.3.4 The Impact of Gram-Negative Bacteria

All the most frequent foodborne bacteria, including campylobacter, salmonella and yersinia are labelled as Gram negative [24]. This designation is related to the reaction of those bacteria to the process of Gram staining and implies that the bacteria are protected by a membrane that produces endotoxins when attacked [24]. It has been hypothesized that infection with Gram negative bacteria might make the intestinal walls more porous, allowing the endotoxins produced by the pathogen as well as by other commensal Gram negative bacteria to reach the circulatory system, a condition known as “leaky gut” syndrome [40]. The presence of those endotoxins in the blood stimulates an

immune response, which causes the release of pro-inflammatory cytokines and the development of the previously explained “Sickness Behaviour” [41].

2.3.5 Potential Effect Modifiers

Both IBS and antibiotic use have been associated with an altered gastrointestinal microbiota [39, 42, 43]. While some FBIs have been linked with durable modifications of the microbiota [36, 37], their impact on a microbiota that is already altered by IBS or antibiotic use is uncertain. As gut dysbiosis is one of the mechanisms through which FBIs can influence the risk of developing DD, it is relevant to verify if the relationship between FBIs and DD is the same in patients with pre-existing IBS or antibiotic use, and those without. As for sex as an effect modifier, an RCT has demonstrated that in women, exposure to 0.8 ng/kg of body weight of the Escherichia Coli endotoxin is associated with a greater increase in depressed mood than in males [44]. The same threshold of pro-inflammatory cytokines also appears to have more impact on the mood of women compared with men [44]. Thus, it is relevant to assess whether sex influences the likelihood of developing DD as a sequela of an FBI.

3. OBJECTIVES AND HYPOTHESES

3.1 Primary Objective

The primary objective of this thesis is to determine whether laboratory-confirmed exposure to an FBI increases the risk of a subsequent diagnosis of DD in the general population, compared with individuals with no confirmed FBI exposure.

3.1.1 Secondary Objectives

Two secondary objectives have been defined in this thesis:

1. To determine and compare the impact of the six most frequent individual foodborne pathogens in BC on the risk of developing DD.
2. To determine whether sex, antibiotic exposure or the presence of an IBS diagnosis prior to FBI exposure are effect modifiers.

3.2 Hypotheses

The primary hypothesis is that laboratory-confirmed FBI exposure is associated with an increased risk of DD in the general population.

The secondary hypotheses are:

1. The association is stronger when the individual pathogen responsible for exposure is a gram-negative bacterium.
2. There is effect measure modification by sex, with women having an increased risk of DD compared to men. Antibiotic exposure and prior IBS status as effect modifiers might make the association between FBI exposure and DD either stronger or weaker.

4. METHODS AND ANALYSES

This chapter will provide more details about the methods that are described in the manuscript included in Chapter 4 of this thesis, as well as explanations of the rationale behind the data handling and extraction choices that were made.

4.1 Data Source

Population Data BC is a " multi-university data and education resource that supports data linkage and access to individual-level, de-identified data for research on the determinants of human health, well-being and development" [45]. The data brokered by Population Data BC is obtained yearly from a number of provincial and federal agencies and ministries, such as the BC Ministry of Health or Statistics Canada, de-identified and made available to researchers through a Secure Research Environment (SRE) that can be accessed remotely from anywhere in Canada [45]. The core linkage file built by Population Data BC, the "Population Directory" contains all residents of BC, with the exception of those that are covered under a federal health plan, which includes members of the Canadian Armed Forces, members of the Royal Canadian Mounted Police (until 2013), federal prisoners and some first nation members [45, 46]. Researchers using the datasets from Population Data BC thus have access to the data of an almost complete population, which minimizes the risk of selection bias [47].

Canada adheres to a universal health coverage model that is publicly funded and provincially managed. Under the Canada Health Act, all medically necessary hospital, diagnostic and physician services are covered for all residents and from the first dollar by the provincial public health insurance program [48]. For other services, such as the provision of prescriptions and dental care, an out-of-pocket payment might be required from the patient [48]. The presence of universal health coverage ensures that cost is not a barrier for any residents to access physician services, which minimizes the risk of a diagnostic/treatment access bias in the data collected by Population Data BC [47].

Due to the completeness of the data brokered and the extensive linkages between various databases containing variables of interest, the Population Data Bc databases were considered to be a valid source to investigate the research question explored in this thesis. The data used in this thesis was extracted from six provincial-level administrative health databases and one surveillance database from BC that were linked at the individual level by Population Data BC [45, 49]:

1. The BC Medical Services Plan (MSP), that includes all fee-for-service physician visit [50];
2. The BC Discharge Abstracts Database (DAD), that includes all hospitalizations [51];
3. BC Vital Statistics (VS), that includes all deaths [52];
4. PharmaNet, that includes every prescription dispensed in BC, irrespective of the payer (except to treat HIV) [53];
5. The Consolidation File that includes patient demographics (e.g. age, sex) [54];
6. Income band data [55]; and
7. Panorama, BC's surveillance system that includes all laboratory-confirmed FBIs in BC.

Cases of DD and IBS were identified using the data available in databases 1 and 2. Those two databases were also used to identify the comorbidities that were adjusted for using the Charlson Comorbidity Index. Database 3 was used to censor patients at the moment of their death. Database 4 was used to detect the use by individual patients of prescription medications of interest that were considered in the calculation of the propensity score. Databases 5 and 6 contain demographic and income band data that was also taken into account in the computation of the propensity score. Finally, database 7 captures all laboratory-identified cases of FBIs that occurred in BC during the study period.

The data was stored and analysed in Population Data B.C.'s virtual SRE. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all data preparation and analyses.

4.2 Study Cohort

The BC population (~4.7 million circa 2014) was the source population for this study. The sampling frame contained all the BC residents that were covered by the provincial Medical Service Plan (MSP) during the study period, which ran from Jan. 1, 2005 to Dec. 31, 2014 inclusive. As it is mandatory for all BC residents and their dependents to enrol with the MSP [32], it is reasonable to assume few BC residents were missing in the administrative database, aside from those that are covered under a federal health plan. An open cohort design was used, so anyone who moved to BC or was born in BC during the study period was included in the sampling frame (provided they were covered by the MSP).

The study cohort comprised all individuals with laboratory-confirmed exposure to an FBI as well as their unexposed matches, selected within the sampling frame. Exposed individuals who fulfilled the criteria of a DD in the 2 years prior to their FBI were excluded from the cohort prior to matching, as they were considered to be outcome-positive before the studied exposure. Unexposed individuals were also excluded as possible matches if they fulfilled the criteria of a DD at any point during the previous two years. Both exposed and unexposed were excluded from the matching set if they were not covered by the MSP at the date of the FBI/matching (uncovered exposed individual can still appear in the Panorama surveillance dataset, as their infection is a reportable disease).

To identify and exclude individuals who were diagnosed with DD before the beginning of the study period, the data for a two-year 'wash in' period was obtained (Jan. 1, 2003 to Dec. 31, 2004). Data was also obtained for a two-year 'wash out' period (Jan. 1, 2015 to Dec. 31, 2016) to detect cases of DD in individual who were diagnosed with an FBI towards the end of the study period.

4.3 Exposure

The criterion for an individual to be considered as exposed was a diagnosis of one of the following FBIs, confirmed by laboratory results and reported to the provincial authorities: *Campylobacter, Clostridium botulinum*, Cryptosporidium, Cyclospora, Giardia, Hepatitis A, *Listeria*, *Salmonella spp.* (non-typhoidal, Typhi, Paratyphi), Shiga Toxin–Producing Escherichia Coli (STEC), *Shigella*, *Vibrio parahaemolyticus*, and *Yersinia (excluding Pestis).* The choice of those 14 infections was

based on the fact that they are reportable in BC and encompass almost all cases of FBIs in the province [26]. It was possible for an exposed individual to be infected by more than one pathogen at the same time (co-infected) or to have multiple FBI exposures over the study period (repeatedly infected). The main analysis included individuals with only one exposure to a single foodborne pathogen over the study period. Co-infected and repeatedly infected individuals were added in sensitivity analyses. In the case of individuals who were repeatedly infected, DD as a sequela was associated to the last FBI before they became outcome positive.

4.4 Outcome

To determine whether individuals developed DD, I used the ICD diagnostic codes within the MSP and DAD data, together with a validated coding algorithm. Specifically, the case definition I used for DD was either two depression claims with depression ICD codes within a one-year window or one hospital DAD depression diagnosis in the last two years. The ICD-10 codes that were used to identify cases of DD in the DAD data were F20.4, F31.3-F31.5, F32.x, F33.x, F34.1, F41.2 and F43.2. The ICD-9 codes that were used to identify cases of DD in the MSP data were 296.2, 296.3, 296.5, 300.4, 309.x and 311. Patients who became outcome-positive were censored at the first month during which either of the two criteria were met. This algorithm has been validated on BC's administrative health data by Doktorchik and yielded a moderate sensitivity of 62.4% and a high specificity of 92.7%. The positive predictive value was 61.7% and the negative predictive value was 92.8% [56].

The choice of this algorithm is further supported by the fact that it is similar to the case definition proposed by the British Columbia Center for Disease Control (BCCDC) for detecting depression in administrative data, which requires the presence of either two physician claims with depression ICD codes or one hospitalization with a depression diagnosis within a one-year window and suggest using the codes F32.x (single depressive episode) and F33.x (recurrent depressive disorder) when using ICD-10 codes or 296.x (affective psychoses), 311.x (depressive disorder) and 50B (anxiety/depression) when using ICD-9 codes [57]. Code 50B is a diagnostic code that is specific to BC, so it is not captured in algorithms elaborated outside of the province. It is a catch-all code that is used in MSP billing to code for both anxiety and depression [57]. As code 50B can also be

used for anxiety, which is not an outcome that is of interest for this thesis, the choice was made to not add it to the algorithm developed by Doktorchik in order to maintain a high degree of specificity.

In accordance with the BCCDC proposed case definition, both primary and secondary diagnosis codes recorded in the MSP claims or DAD were used in the algorithm.

4.5 Covariates

4.5.1 Demographic Characteristics

Due to demographic/geographical variations in the incidence of FBIs, age, sex, income decile and local health authority were included in the calculation of the propensity score using data from the Consolidation file and from the Income Band Data file

4.5.2 Comorbidities

Comorbidities such as cancer, diabetes and renal failure have all been identified as risk factors for contracting an FBI [58, 59]. In order to adjust for the presence of those comorbidities, which might be more common in individuals with a laboratory-confirmed exposure to an FBI, the Charlson Comorbidities Index (CCI), an aggregated comorbidity score, was included in the calculation of the propensity score.

Two different methodologies exist for calculating the CCI: the weighted index and the counting of comorbid diseases (unweighted index). For the calculation of the weighted CCI, a weight from 1 to 6 has been attributed to each of the 19 individual Charlson comorbidities, based on the 1 year relative risk of death associated with the comorbidity in the Charlson study, with a higher weight being attributed to comorbidities bearing a higher relative risk of death [60]. The weighted CCI is obtained by summing up the weight of each of the comorbidities presented by an individual. An unweighted CCI can also be calculated by simply summing up the number of Charlson comorbidities presented by a patient, giving a weight of 1 to each comorbidity [60]. The CCI can also include an age component, with the addition of one point per decade to the index, starting at age 50 [61].

Due to its simplicity of use and its proven validity as a measure of comorbidity [60], the CCI was deemed an appropriate measure of comorbidity to use in this study. As demonstrated by Austin, use of the CCI in a model is equivalent to integrating all comorbidities individually and thus, allows for a simpler model [62]. The CCI was computed using all diagnoses codes in the MSP and DAD for the 12 months prior to matching and was included as a continuous variable in the calculation of the propensity score to adjust for comorbidities. Deyo's ICD-9 coding algorithm was used to extract data on the relevant conditions from the MSP [63]. The standard ICD-10 coding algorithm was used to extract data from the DAD [63]. The weighted CCI was used in this thesis as it considers the severity of the comorbidities presented by a patient as well as the number of comorbidities. The age-unadjusted CCI was selected because age was already adjusted for both through exact matching and through inclusion in the calculation of the propensity score. In the case a patient had both codes related to diabetes without chronic complications and to diabetes with chronic complications in the same 12 months period, only diabetes with chronic complications was included in the calculation of the CCI, as those conditions were considered to be mutually exclusive.

4.5.3 Medication

Due to their impact on gut microbiota, multiple classes of medications have been found to alter the risk of developing a foodborne illness, both in human and animal studies [42, 59, 64-66]. Thus, exposure to the three classes of medication that were found by Imhann et al. to have the most impact on inter-individual gut microbiota variation was included in the calculation of the propensity score [42]. On the advice of a pharmacist, aside from Proton-Pump Inhibitors, Statins and Antibiotics, I included immunosuppressive agents and immunomodulatory agents in the calculation, as prolonged use of these medications has been associated with the development of opportunistic infections, including FBIs [42, 67, 68].

Exposure to the five selected medication classes was defined as a binary variable for each. Individuals who had filled a prescription which, if taken as instructed, would overlap over the three months period prior to exposure to an FBI, including the month of declaration of the FBI, were considered as exposed to that medication, except for antibiotics and PPI. For those two specific

medication classes, only exposure in the two months prior to the month of declaration was considered. For antibiotics, initial exposure in the month of declaration of the FBI was excluded due to the fact that the antibiotic could have been prescribed to treat the FBI rather than prior to it, which would cause temporality issues in the calculation of the propensity score. In the case of PPIs, as they are frequently prescribed to hospitalized patients or when a patient is discharged from the hospital [69], they could have been prescribed at the occasion of a hospital visit due to an FBI, which would also cause temporality issues. As statins, immunosuppressive and immunomodulatory agents are extremely unlikely to be prescribed when a patient consults for an FBI, the month of declaration of the FBI was not excluded for those medications.

Exposure was identified thought the Pharmanet data using the Drug Identification Numbers (DINs) associated with each of the five drug classes, based on the American Hospital Formulary Service (AHFS) classification [70]. DINs associated with topical, ophthalmic and otic antibiotics were excluded from our list of DINs by a pharmacist, as those drugs are unlikely to have a systemic impact due to the very low serum concentration observed after administration through those routes [71-73].

While the impact of the selected medications classes on the gut microbiota and the likelihood of developing an FBI could possibly be mitigated by the dosage prescribed or the length of treatment, the scarcity of previous literature on the subject prompted the decision to include any exposure, regardless of dosage or length of treatment.

4.5.4 Prior IBS Status

IBS is a GI condition of which the main symptoms are abdominal pain, GI dysmotility and visceral hypersensitivity [74]. This condition has been associated with a greater frequency of certain psychological conditions, namely anxiety, somatisation, depression and neuroticism, but it is not a systematic association [7, 74]. No biomarker is consistently present in IBS patients, so physicians have to rely on diagnostic scales, such as the Rome criteria to identify IBS in their patients [74].

IBS was assessed as an effect modifier due to the increased frequency of DD in IBS patients [7, 74] and was detected in the MSP using ICD-9 code 564.1 and in the DAD using ICD-10 codes

K58.0 and K58.9 [75]. As IBS can be considered to be a chronic disease [74], patients were classified as IBS-positive from the moment of their first IBS diagnosis in either the MSP or the DAD until the end of the study period. As for DD, both primary and secondary diagnosis codes were considered for the identification of IBS.

4.6 Statistical Analysis

4.6.1 Matching Process

FBI exposed patients were matched 1:4 at the date of their laboratory confirmed infection on sex, exact age, month, year and length of uninterrupted MSP coverage prior to the matching with unexposed patients (12 month or less, 13 to 24 months, 25 months or more), without replacement. I selected four unexposed matches for each exposed individual in an attempt to balance the advantage of less sampling variability inherent with a greater number of unexposed matches and the computational demand required to handle a greater matching fraction.

Before the matching procedure, the unexposed group was randomly divided into 120 equal subgroups, which correspond to one subgroup for each month of the 10 years study period. Each subgroup was assigned to one month of the study period and individuals in that subgroup could only be matched to exposed patient whose FBI was confirmed in that month. This procedure was performed to guarantee matching without replacement and to ensure that the number of unexposed individuals available to be matched to an exposed patient did not differ based on how close to the end of the study period their exposure occurred.

4.6.2 Propensity score calculation

Propensity scores can be used to correct for confounding by indication (probability of being exposed), as they adjust for the characteristics present in individuals at the moment of exposure. This adjustment creates a pseudo-randomization in an observational study [76]. In this study, the propensity score for the probability of FBI exposure was estimated using the following factors, which have all been hypothesized to influence the risk of developing an FBI, as independent variables: age, sex, income decile, LHA, recent exposure to antibiotics, PPIs, statins, immunosuppressive agents, immunomodulatory agents and CCI [42, 44, 58, 59, 64-68]. While sex

and age were already adjusted for through matching, those variables were still included in the calculation of the propensity score, as the stratification analyses performed could possibly impact the balance in those covariates achieved through matching [77].

4.6.3 Cox Proportional Hazard Regressions

I performed Cox proportional hazard regression analysis on the matched sample to estimate the hazard ratio of developing depression as a sequela of an FBI. The time variable used in the Cox models was time since FBI/matching. Both a crude and an adjusted model were fitted for each of the regression analyses. The propensity score was used as a continuous adjustment factor in our adjusted model, as it enabled for more precise control for confounding than simply using propensity score quintiles [78]. As all available relevant covariates were included in the propensity score calculation and as propensity score adjustment has been found to give similar results to a fitted model controlling for the same covariates, no other covariates were included in the model [77].

Pathogen-specific hazard ratios were calculated for all pathogens that accumulated more than 1000 cases over the study period. For pathogens with a lower number of cases, calculating a pathogen-specific hazard ratio would not have been informative as the low number of exposed individuals would result in a very large confidence interval. As the patient profile and risk factors are different for each of the pathogens, the propensity score was recalculated for each of the pathogen-specific analyses to capture the risk factors specific to the analysed pathogen.

Sensitivity analyses were performed to evaluate the impact of adding exposed patients who were co-infected or repeatedly infected and their unexposed matches to the sets. In the first sensitivity analysis, only patients with one single FBI episode over the study period, no matter the number of pathogens simultaneously involved, were included. In the second sensitivity analysis, all MSP-covered patients with reported FBI exposure were included. Repeatedly infected patients were censored after each FBI episode at month of onset of the next FBI and had 4 different unexposed matches for each of the FBI episodes.

To address the secondary objective of determining whether sex, antibiotic exposure and IBS status prior to FBI are effect modifiers, the hazard measures were stratified based on those variables.

5. MANUSCRIPT

This chapter contains the manuscript of the study exploring the association between laboratory-confirmed FBI exposure and the development of DD. This manuscript is intended to be submitted to the Brain, Behavior, and Immunity journal and has been formatted as per the specifications of the journal.

Original Research Article

Foodborne Infections as a Risk factor for Depressive Disorders – A Retrospective Population-Based Study

Valerie C. Rodrigue [1], Erica E.M. Moodie [1], Eleni Galanis [2,3], Shannon E. Majowicz [4], Marsha Taylor [2], Dimitra Panagiotoglou [1]

[1] Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada

[2] British Columbia Centre for Disease Control, Vancouver, British Columbia, Canada

[3] School of Population and Public Health, The University of British Columbia, Vancouver, British Columbia, Canada

[4] School of Public Health and Health Systems, University of Waterloo, Waterloo, Ontario, Canada

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Correspondence:

Dr Dimitra Panagiotoglou

Department of Epidemiology, Biostatistics and Occupational Health

McGill University, Purvis Hall, room 47B

1020 Pine Avenue West

Montreal, Quebec, H3A 1A2

Telephone : 514-398-8451

Email : dimitra.panagiotoglou@mcgill.ca

5.1 Abstract

Background: Gut dysbiosis has been hypothesized as a risk factor for depression. However, few studies have explored the role of infection by foodborne illnesses (FBIs) in the development of depressive disorders (DD) and studies with laboratory-confirmed pathogen identification are lacking. The aim of this study was to determine whether exposure to fourteen common FBIs (botulism, Campylobacter, Cryptosporidium, Cyclospora, Giardia, Hepatitis A, Listeria, Salmonella spp. (non-typhoidal, Typhi, Paratyphi), Shiga Toxin–Producing Escherichia Coli (STEC), Shigella, Vibrio parahaemolyticus, and Yersinia) increases the risk of DD.

Methods: Using administrative health data provided by Population Data BC, we conducted a retrospective, population-based matched cohort study among 33,360 individuals who were listed in British Columbia's reportable disease system as exposed to one of the FBIs of interest between Jan. 1, 2005 and Dec. 31, 2014 as well as 133,068 unexposed individuals, matched 4:1 with the exposed individuals on sex, exact age, month, year and length of uninterrupted health insurance coverage. Cox proportional hazard models were used to estimate the hazard ratios and 95% confidence intervals of DD incidence following exposure to one of the 14 FBIs. Sex, prior IBS status and exposure to antibiotics were assessed as possible effect-modifiers.

Results: FBI exposure was associated with a 38% increased hazard ratio (HR) of depression in the adjusted model (HR 1.38, 95%CI 1.33-1.43), compared with individuals without laboratory-confirmed FBI exposure. Of the six most frequent pathogens, only STEC was not significantly associated with a higher risk of developing DD (HR 1.15, 95% CI 0.93-1.42). Sex and prior IBS status were not found to be significant effect modifiers.

Conclusions: In this first large study with laboratory-confirmed pathogen identification, FBI exposure was associated with an increased risk of a subsequent depression diagnosis. More research is needed to uncover whether this association is attributable to the perturbation of the microbiota by foodborne pathogens or to other biological and psychological factors.

5.2 Introduction

Depressive Disorders (DD), colloquially referred to as depression, are a group of mental health conditions mainly characterised by depressed/irritable mood and loss of interest in most activities. Patients can also experience changes in appetite and sleeping patterns, fatigue, psychomotor agitation or retardation, decreased concentration, feelings of worthlessness and recurrent thoughts of death/suicidal ideation. (American Psychiatric Association 2013). According to the Global Burden of Disease Study of 195 countries and territories, Major Depressive Disorder (MDD), the main and most severe diagnosis of the DD group, is the fifth leading cause of years lived with disability (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017). Based on the results of the Canadian Community Health Survey, the Conference Board of Canada estimated the loss in worker productivity due to DD has cost the Canadian economy $32.3 billions in foregone gross domestic product (Conference Board of Canada 2016).

The etiology of DD is complex and involves a number of interacting biological, genetic, psychological and environmental risk factors (Beck and Bredemeier 2016; Chiriță 2015). The composition of the gut microbiota has been found to be significantly different in depressed and non-depressed individuals and perturbations of the microbiota (dysbiosis) are hypothesized to have an impact on the mental health of patients in a number of ways (Inserra et al. 2018; Rogers et al. 2016). Infection of the gut by foodborne pathogens, such as campylobacter and giardia, has been demonstrated to modify the microbiota composition (Dicksved et al. 2014; Berry et al. 2020). Infections in general and the resulting inflammatory process can also triggers an adaptative response to disease known as “Sickness Behaviour”, that causes symptoms similar to those of depressive disorders, such as depressed mood, disturbed eating/sleeping pattern and lack of desire to socialize (Dantzer 2009; Patterson 2011). In individuals with a predisposition to DD, sickness behaviour has been hypothesized to be linked with the development of depressive mood persisting after the healing of an infection (Dantzer 2009). Meanwhile, Gram-negative bacteria such as Shiga Toxin–Producing Escherichia Coli (STEC) can contribute to the development of the “leaky gut” syndrome, a condition in which endotoxins produced by the pathogen and other commensal bacteria present in the gut are released in the blood, stimulating an immune response and the production of pro-inflammatory cytokines, which can trigger sickness behaviour (Maes, Kubera, and Leunis 2008; Kalischuk, Leggett, and Douglas Inglis 2010). DD have also been linked with

inflammation related to non-infectious conditions and are frequently associated with inflammatory comorbid conditions, such as IBS, arthritis, diabetes and obesity (Fond et al. 2014; Dantzer and Capuron 2017). Stressful life events are a another risk factor for DD, especially when they are perceived as negative or uncontrollable (Gómez Maquet et al. 2020). Because of the incapacitating and sudden nature of FBIs, it is extremely likely that they will be perceived as negative and uncontrollable by patients. Hence, due to their impact on the microbiota, the immune activation they cause and the mental stress they generate, foodborne illnesses (FBIs) are likely to increase the risk of DD in patients.

Among the few studies that have explored the hypothesis of DD as a sequela of an FBI (Benros et al. 2013; Lowe et al. 2014; Parent et al. 2019), none to our knowledge used laboratory-confirmed identification of the pathogens and followed patient mental health for longer than six months post FBI infection. We conducted a population-based retrospective matched cohort study using "individual-level longitudinal data from [six] province-wide administrative health [databases] and [one] reportable disease database"(Majowicz et al. 2020) from British Columbia (BC), Canada, to investigate whether laboratory-confirmed FBIs are associated with a greater risk of developing DD. We also assessed the impact of irritable bowel syndrome (IBS) and antibiotic exposure in the 2 months prior to the FBI as effect modifiers of the relationship between FBI exposure and DD, and explored the impact of each of the most common pathogens on the risk of developing DD, individually.

5.3 Methods

5.3.1 Data source

Data from six provincial administrative health databases were de-identified and linked at the individual-level with BC's reportable disease system data by Population Data BC, a " multi-university data and education resource that supports data linkage and access to individual-level, de-identified data for research on the determinants of human health, well-being and development" (Ark et al. 2020). Together, the Medical Services Plan (MSP) (British Columbia Ministry of Health [creator] 2018), Consolidation File (British Columbia Ministry of Health [creator] 2019a), Discharge Abstracts Database (DAD) (Canadian Institute for Health Information 2019), Vital Events and Statistics: Deaths (VS) (British Columbia Vital Statistics Agency [creator] 2019),

PharmaNet (British Columbia Ministry of Health [creator] 2019b), and BC reportable disease system datasets captured all fee-for-service physician visits, hospitalizations, deaths, prescriptions dispensed, and laboratory-confirmed cases of foodborne infections that occurred between January 1 2005 and December 31 2014 (Population Data BC ; BC Centre for Disease Control).

5.3.2 Study population

All BC residents (~4.7 million circa 2014) enrolled in the provincial Medical Services Plan at some point during the study period were included in the study population. Enrollment in the MSP is mandatory for all BC residents with the exception of members of the Canadian Armed Forces, Royal Canadian Mounted Police (until 2013) and some First Nations members who are covered under federal health plans (British Columbia Ministry of Health 2019). An open cohort design was used, so anyone who moved to BC or was born in BC during the study period was included.

5.3.3 Exposure: Foodborne Illnesses

Individuals were classified as exposed to a FBI if they had a laboratory-confirmed, provincially-reported infection with one of the following pathogens during the study period: Campylobacter*, Clostridium botulinum*, Cryptosporidium, Cyclospora, Giardia, Hepatitis A, Listeria, *Salmonella spp.* (non-typhoidal, Typhi, Paratyphi), STEC, Shigella, *Vibrio parahaemolyticus*, and Yersinia (excluding Pestis). Patients who had infections with two or more different pathogens reported in the same calendar month were considered as co-infected with both pathogens and patients with multiple reported infections with either the same pathogen or different pathogens that were not reported in the same calendar month were considered repeatedly infected.

5.3.4 Outcome: DD diagnosis

Data on depressive disorders in patients were obtained through the MSP and DAD datasets. Patients were defined as outcome-positive if they had either two physician claims (ICD-9 CM codes: 296.2, 296.3, 296.5, 300.4, 309.x, and 311) within one year or one hospitalization record (ICD-10: F20.4, F31.3-F31.5, F32.x, F33.x, F34.1, F41.2, and F43.2) within two years (Doktorchik et al. 2019). The month of onset was defined as the first month during which either of the two criteria was met. Both the primary and secondary diagnoses codes recorded in each MSP claim or DAD were used in the algorithm.

Persons who fulfilled the criteria for DD prior to FBI exposure were considered ineligible for inclusion, using a two year 'wash-in' period (January 1 2003 to December 31 2004) for individuals who were diagnosed with an FBI at the beginning of the study period. Individuals without a laboratory-confirmed FBI (unexposed) who met the criteria for DD were excluded as possible matches until 24 months after the last point in time they fitted the DD case definition. A two-year 'wash out' period (January 1 2015 to December 31 2016) was applied to detect cases of DD in individual who were diagnosed with an FBI at the end of the study period.

5.3.5 Covariates

Demographic covariates including age, sex, local health authority (LHA) and income decile were extracted from the consolidation file and income band data file (Statistics Canada [creator] 2018) provided by Population Data BC. Missing income decile or local health area values were replaced by the default '99' and '999' values used by Population Data BC.

The Charlson Comorbidities Index (CCI), an aggregated comorbidity measure calculated by adding up the weight attributed to each of the patient's conditions and used to measure morbidity (Charlson et al. 1987), was also included in the calculation of the propensity score. It was used to adjust for the presence of comorbid conditions such as cancer, diabetes and renal diseases, which might be more common in individuals with a laboratory-confirmed exposure to an FBI as those conditions are a risk factor for infections (Hohmann 2001; Mook, O'Brien, and Gillespie 2011). We computed the CCI using all diagnoses included in the physician billing (MSP) and hospitalization records (DAD) covering the 12 months prior to entry in the study. Quan's algorithms were used to detect the comorbidities included in the CCI, which were weighted based on the weights attributed in the original Charlson study (Charlson et al. 1987; Quan et al. 2005). The CCI was included in the calculation of the propensity score as a continuous covariate.

Information on exposure to antibiotics, proton-pump inhibitors (PPIs), statins, immunomodulatory agents and immunosuppressive agents was extracted from Pharmanet using a pharmacist-reviewed list of the drug identification numbers (DINs) associated with each of the five drug classes, based on the American Hospital Formulary Service (AHFS) classification (American Society of Health-System Pharmacists Inc. 2019). Topical, otic and ophthalmic antibiotics were excluded due to their minimal systemic effects. The list of all pharmaceutical products included is shown in supplemental

Table 1. Exposure was defined as a binary variable and ascertained as having an active prescription for the product in the three months prior to the date an FBI was reported, including the month of reporting, except for antibiotics and PPI. For those two classes of medication, only the two months before the month of reporting were considered. Exposure to antibiotics and PPI during the month the FBI was reported was not considered in order to avoid including a prescription that was dispensed to treat an FBI or during an hospital visit related to an FBI rather than prior to the FBI, which would cause temporality issues in the calculation of the propensity score.

Antibiotics, PPIs and statins were selected as covariates because of their documented impact on the intestinal microbiota and their influence on the risk of developing an FBI (Augustin et al. 2021; Bavishi and Dupont 2011; Hohmann 2001; Imhann et al. 2017; Parihar et al. 2013). Immunomodulatory and immunosuppressive agents were included based on the pharmacist's recommendation given long-term use has been associated with the occurrence of opportunistic infections (Chen et al. 2018; Toruner et al. 2008).

Due to the exploratory nature of this study and the scarcity of previous literature on the subject, the impact of dosage and length of treatment were not explored.

The presence of IBS, which was assessed as an effect modifier due to the association between IBS and DD (Fond et al. 2014), was detected by using ICD-9 code 564.1 in the MSP data and ICD-10 codes K58.0 and K58.9 in the DAD (Goff et al. 2008). We considered IBS as a chronic illness with patients classified as IBS-positive from the month of their first diagnosis in either the MSP or the DAD until the end of the study period.

5.3.6 Statistical Analysis

We conducted a retrospective, matched cohort study. FBI exposed patients were matched 1:4 at the date their laboratory confirmed infection was reported on sex, exact age, month, year and length of uninterrupted MSP coverage prior to the matching with unexposed patients (12 month or less, 13 to 24 months, 25 months or more), without replacement.

After exact matching, we created a propensity score for the probability of FBI exposure using age, sex, income decile, LHA, recent exposure to antibiotics, PPIs, statins, immunosuppressive agents, immunomodulatory agents and CCI. While sex and age were already adjusted for through matching, we still included them in the calculation of the propensity score, as the stratification

analyses we performed could possibly impact the balance in those covariates achieved through matching.

We performed Cox proportional hazard regression analysis on the matched sample to estimate the hazard ratio of developing depression as a sequela of an FBI. The propensity score was used as a continuous adjustment factor in our Cox regression, as it allowed us to adjust for multiple baseline covariates with only one variable, decreasing the risk of overfitting the model. As all available relevant covariates were included in the propensity score calculation and as propensity score adjustment as been found to give similar results to a fitted model controlling for the same covariates, no other covariates were included in the model (DAgostino 1998). The adjusted model thus included only exposure to an FBI and propensity score as explanatory variables. We stratified our hazards measures by sex, antibiotic exposure and pre-existing IBS.

Secondary analyses estimated the pathogen-specific hazard ratios for all pathogens with more than 1,000 cases reported in BC's reportable diseases system during the study period. As the risk factors of contracting an FBI might differ for each individual pathogen, the propensity score was recalculated for each pathogen-specific analysis.

Sensitivity analysis were performed to evaluate the impact of adding exposed patients who were co-infected or repeatedly infected and their unexposed matches to the sets. Repeatedly infected patients were censored at month of onset of the next FBI. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

5.4 Results

The matched cohort contained 33,360 (46.5% of whom were females) exposed individuals and 133,068 unexposed controls for a total of 166,428 individuals followed from the month of matching until the development of DD, death, loss of MSP coverage, or December 31, 2016. There were 222 exposed individuals in the matched cohort who had less than four unexposed matches, but they all had at least one. The average age of FBI exposure was 37.8 years old (SD ± 22.9 years). During a mean follow-up period of 5.80 years, 4,515 (23.7 per 1000 person-years) incident cases of DD were detected in the exposed patients and 12,273 (15.8 per 1000 person-years) in the unexposed patients for a total of 16,788 incident cases of DD (58.5% among females) over nearly 965,280

person-years of follow-up. The distribution of baseline characteristics among FBI exposed and non-exposed patients is displayed in Table 1.

5.4.1 Overall Risk

Exposure to any laboratory-confirmed FBI was associated with a hazard ratio (HR) of 1.38 (95% CI 1.33-1.43) of developing DD compared to individuals who did not have a laboratory-confirmed FBI in the adjusted model (Table 2). In females, exposure to an FBI was associated with an adjusted HR of 1.37 (95% CI 1.31-1.43), and in males 1.41 (95% CI 1.33-1.48). The difference in HR between females and males was not significant (p=0.42).

5.4.2 Specific Pathogens

We detected an increased risk of developing DD following Campylobacter (HR 1.36, 95% CI 1.28-1.44), Non-Typhoidal Salmonella (HR 1.40, 95% CI 1.29-1.52), Giardia (HR 1.34, 95% CI 1.21-1.48), Yersinia (HR 1.58, 95% CI 1.44-1.74) and Shigella (HR 1.55, 95% CI 1.30-1.85) infections. STEC could not be formally associated with a higher risk of developing DD as statistical significance was not reached (HR 1.15, 95% CI 0.93-1.42). Yersinia was associated with a significantly higher risk of developing DD than other FBIs (p<0.0001). Other pathogens had less than 1000 cases reported in BC's reportable diseases system and were not individually analysed.

5.4.3 IBS as an effect modifier

Among those matched, 590 patients in the exposed group and 26 patients in the unexposed group had an IBS diagnosis prior to exposure/matching for a total of 616 IBS-positive subjects. Exposed patients with IBS had a 30% increased hazard of developing DD (adjusted HR=1.30, 95% CI 0.48-3.51) while exposed patients without IBS had a 36% increased hazard of developing DD following FBI (adjusted HR=1.36, 95% CI 1.32-1.41) (p=0.92) compared with respective unexposed matches.

5.4.4 Antibiotic exposure as an effect modifier

When stratifying on antibiotic exposure in the two months prior to the FBI, we found a lower HR of developing DD (HR=1.14, 95% CI 1.01-1.28) in individuals exposed to antibiotics compared with individuals who were not exposed (HR 1.40, 95% CI 1.35-1.46) (p<0.0001).

5.4.5 Sensitivity Analyses

A total of 707 eligible individuals were coinfected with two or more foodborne pathogens at the time of their lab confirmed diagnosis. When we added these individuals to the cohort, we found an almost unchanged hazard of developing DD (adjusted HR 1.39, 95% CI 1.34-1.44).

A total of 1637 eligible individuals were found to be coinfected with two or more foodborne pathogens and/or repeatedly infected over the study period. When we added the episodes of FBI of those individuals to the cohort, the HR remained qualitatively unchanged (HR 1.39, 95% CI 1.34-1.44).

5.4.6 Number Needed to Treat

For a mean follow-up period of 5.80 years after exposure to an FBI, the number needed to treat is 31, which means that for 31 cases of FBI avoided, 1 less patient will develop DD.

5.5 Discussion

In this retrospective matched cohort study, we found that individuals with a laboratory-confirmed case of FBI had a 38% increased risk of subsequent DD-related physician claim or hospitalisation; with no notable difference between males and females. Campylobacter, Non-Typhoidal Salmonella, Giardia, Yersinia and Shigella were significantly associated with subsequent DD, individually. IBS status prior to the FBI did not differentially impact the risk of developing DD following exposure.

Previous studies have found an increased risk of developing mood disorders or emotional difficulties after exposure to gastro-intestinal (GI) infections, which is in line with our findings using laboratory-confirmed exposure (Benros et al. 2013; Lowe et al. 2014; Parent et al. 2019). Benros reported an incidence rate ratio (IRR) for mood disorders of 1.62 (95%CI 1.58-1.66) among persons with a hospital contact for a GI infection, adjusted for sex, age, calendar period and other infections. This is slightly higher than our own IRR of 1.50 (95%CI 1.45-1.55) (23.7 per 1000 person-years/15.8 per 1000 person-years) among persons with a laboratory confirmed FBI, adjusted for sex, age, month, year and length of uninterrupted MSP coverage through matching. However, as the criterion that defined exposure in the Benros study was a hospital contact due to an infection, it is likely that the exposed patients in that study had a more severe infection on

average than those in our study, which could have impacted their risk of developing DD. Both Lowe and Parent are examining the degree of depressive symptoms in patients rather than the presence of a clinical diagnosis of DD. It is thus difficult to compare our results to theirs.

Although a German study conducted by Lowe et al. after the 2011 fenugreek seeds STEC outbreak found an association between STEC and DD (Lowe et al. 2014), the relationship we observed between STEC and DD was not significant. Notably, the German study focussed on patients who sought care due to bloody diarrhea and/or hemolytic uremic syndrome following infection with one particular strain of STEC (0104). It is thus possible the severity of their symptoms or the strain impacted these patients' risk of developing DD.

Yersinia was associated with a HR of developing DD that was significantly higher than the HR for all other FBIs. When looking at the baseline characteristics, we observed patients infected with yersiniosis were older (42.8 years vs 37.1 for other FBI patients), more likely to be female (54.6% vs 45.4% for other FBI patients), more likely to have comorbidities (19.62% vs 16.95% for other FBI patients), and more likely to have a diagnosis of IBS prior to their exposure to an FBI (2.5% vs 1.7% for other FBI patients). Since the typical patient profile of Yersinia is different from that of all other FBIs, it is possible that part of the difference in hazard could be attributable to unmeasured confounding.

Further, Yersinia may be a spurious finding when investigating the condition of people with chronic GI conditions such as IBS. These conditions are associated with an increased risk of DD (Fond et al. 2014) and can be somatic manifestations of psychiatric conditions (Prospero et al. 2021; Sayuk et al. 2007). It is thus possible that patients diagnosed with yersiniosis are more likely to also suffer from chronic GI problems that increase their risk of developing DD, which is coherent with the fact that a greater percentage of patient exposed to yersinia in our study had a pre-existing diagnosis of IBS.

Having a prior diagnosis of IBS was not associated with a higher HR of developing DD following an FBI, despite the established association between IBS and DD (Fond et al. 2014). However, we had only 590 patients with a prior IBS diagnosis in the exposed group (point prevalence at the time of FBI= 17.69 per 1000) and 26 in the unexposed group (point prevalence at the time of matching= 0.20 per 1000), which most certainly impeded our capacity to evaluate this variable as an effect modifier. Those low numbers could be due to underreporting of cases of IBS in physician claims.

In a study comparing administrative data to survey data, Lix found that only "9.4% of the self-reported IBS cases had an IBS diagnosis [in the physician billing claims in the three years] prior to the interview date" (Lix et al. 2010). Moreover, in a meta-analysis of population-based studies, Lovell estimated the prevalence of IBS to be close to 11.8% in North America (118 per 1000) (Lovell and Ford 2012), which is largely superior to our point prevalence estimates. One possible way to capture a larger number of IBS cases using administrative data could be to add to the algorithm ICD codes of conditions and procedures that are frequently associated with IBS. However, while adding supplementary ICD codes could allow us to capture a greater number of IBS cases, it would most likely decrease the specificity of our algorithm as a tradeoff.

Moreover, the HR of developing DD following FBI exposure among those who were recently on antibiotics is significantly lower than the HR among those not exposed to antibiotics (1.14 vs 1.40). Thus, the FBI-exposed and FBI-unexposed patients who were recently on antibiotics appear to be more similar in their risk of developing DD than those who did not have a recent prescription for antibiotics. As antibiotic exposure has been linked with gut dysbiosis (Francino 2015) and with mood disorders (Kohler-Forsberg et al. 2019), it is possible that exposure to antibiotics increases the likelihood of developing DD, irrespective of FBI exposure. This would be coherent with our observation that 16.32% of the FBI-exposed patient and 13.44% of the FBI-unexposed matches who were exposed to antibiotics developed DD, compared with only 13.26% and 9.09% in the FBI-exposed patients and unexposed matches with no recent exposure to antibiotics (Table 2). However, as Minocycline (Cai et al. 2020) and Ceftriaxone (Bakeer et al. 2019) were recently found to be associated with a decrease in depressive symptoms, further examination will be needed to assess the impact of exposure to different classes and doses of antibiotic as effect modifier of the relationship between FBI exposure and DD.

5.5.1 Strengths and Limitations

The data used for our study was extracted from very large administrative datasets which contain health care utilisation and demographic data for virtually every resident of BC between 2003 and 2016. Such a complete and reliable data source allowed us to adjust our models for comorbidities and medications; and stratify results across important potential modifiers. We were also able to identify enough cases of six pathogens to evaluate their impact individually.

Although relying on laboratory-confirmed cases of FBI increased the specificity of our study, it likely underestimated the overall exposure to FBI in the population. For cases of FBIs to be registered in BC's reportable disease system, patients have to seek care for their symptoms, physicians have to request laboratory testing of their patients' stool samples and the results of these samples have to be correctly recorded (Sundström 2018). Given a significant portion of FBI patients do not seek medical attention/are not asked for samples by their doctors, we can infer that a certain number of our cohort members were misclassified as unexposed. Thomas et al. estimated that in Canada, the multiplier (fraction of all symptomatic cases over reported cases only) is of 27.2 for campylobacter, 26.1 for salmonella, 40.7 for giardia, 39.3 for yersinia and 17.5 for shigella (Thomas et al. 2013). Given those five pathogens constitute almost 90% of our reported cases and assuming our population in BC is similar to that of Canada as a whole, it would be reasonable to expect we are capturing less than 1/25 of the FBI cases in BC's reportable disease system data, most likely the most severe ones. Nevertheless, such misclassification of exposure would tend to bias the results towards the null, which does not threaten the validity of our conclusions.

Due to the use of administrative data, it is also likely that a certain degree of under ascertainment of outcome is present in our study. When validating the case definition for depression that we used, Doktorchik estimated the sensitivity of the algorithm to be around 61.4% and the specificity, around 94,3% (Doktorchik et al. 2019). This indicates that, while most of the patients we identified as having DD were likely correctly identified, approximately 39% of patients who showed indications of DD in their chart might have been overlooked when applying the algorithm to our claim data. We also have to mention the existence in BC of a local claim code for anxiety/depression (50.B), which we ruled against including in the algorithm in order to preserve its specificity, as this code might also be used for anxiety. The code 50.B appears in the claim data of 3,799 outcome-negative exposed patients (19.95 per 1000 person-years) and 11,218 outcome-negative unexposed matches (14.48 per 1000 person-years) between the date of the FBI/matching and the date they were censored. The broadness of symptoms encompassed by code 50.B makes it is difficult to know which proportion of those patients were misclassified as outcome-negative, but in the worst-case scenario that they were all misclassified, the IRR of code 50.B between the exposed and the unexposed would be 1.38 (95%CI 1.33-1.43). While this is slightly lower than our previously calculated IRR of 1,50, it would still confirm that exposed are at greater risk of DD than unexposed. As FBI exposure status is unlikely to influence the choice by the physician to use code

50.B rather than another depression-related code in their claim, we can however expect this misclassification of outcome to be non-differential between exposed and unexposed.

Finally, we also have to consider that patients might avoid discussing depressive symptoms with their physician due the stigma associated with mental health problems and non-psychiatrist physicians might have difficulties to ascertain DD in their patients, resulting in further under ascertainment of DD. A meta-analysis estimated that only 47.3% of case of depression are correctly identified by general practitioners (Mitchell, Vaze, and Rao 2009). Nevertheless, under ascertainment due to underdiagnosis is there again likely to be non-differential, and hence, should not threaten the validity of our results.

5.6 Conclusion

Our findings of a statistical association between exposure to FBI and the development of DD emphasize the need for more research on the biological mechanisms that could be involved in this relationship. The association between the development of DD following an FBI and the presence of chronic physical sequelae of the FBI, such as post-infectious IBS and reactive arthritis, should also be investigated, as long-lasting physical sequelae might impact the risk of developing DD.

ETHICS: This study has been approved by a University of Waterloo Research Ethics Committee (no 30645), the University of British Columbia Behavioral Research Ethics Board (no H16-00021) and McGill University's Institutional Review Board (no A03-M12- 19A) and (no A06-M56-20B).

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Table 2 - Distribution of baseline characteristics of individuals exposed and not exposed to foodborne illnesses

	Exposed to FBI (%)	Unexposed to FBI (%)
Sex		
Female	15,526 (46.54)	61,913 (46.53)
Male	17,834 (53.46)	71,155 (53.47)
Age (SD)	37.84 (22.86)	37.84 (22.86)
Length of MSP coverage		
12 months or less	2119 (6.35)	8258 (6.21)
13 to 24 months	1717 (5.15)	6720 (5.05)
25 months or more	29,524 (88.50)	118,090 (88.74)
Income Quintile		
1	6333 (18.98)	26,389 (19.83)
2	6100 (18.29)	26,730 (20.09)
3	6444 (19.32)	26,388 (19.83)
4	6772 (20.30)	25,859 (19.43)
5	7336 (21.99)	25,525 (19.18)
Missing	375 (1.12)	2177 (1.64)
IBS prior to exposure		
Yes	590 (1.77)	26 (0.02)
No	32,770 (98.23)	133,042 (99.98)
CCI		
0	27,593 (82.71)	119,926 (90.12)
1 to 2	4549 (13.64)	11,836 (8.89)
3 or more	1218 (3.65)	1306 (0.98)
Antibiotic exposure		
Yes	2966 (8.89)	4204 (3.16)
No	30,394 (91.11)	128,864 (96.84)
PPI exposure		
Yes	3692 (11.07)	4087 (3.07)
No	29,668 (88.93)	128,981 (96.93)
Statins exposure		
Yes	2672 (8.01)	8456 (6.35)
No	30,688 (91.99)	124,612 (93.65)
Immunosuppressive exposure		
Yes	268 (0.80)	342 (0.26)
No	33,092 (99.20)	132,726 (99.74)
Immunomodulatory exposure		
Yes	1046 (3.14)	2189 (1.65)
No	32,314 (96.86)	130,879 (98.35)

Table 3 - Distribution of baseline characteristics of individuals exposed and not exposed to Yersinia

	Exposed to FBI (%)	Unexposed to FBI (%)
Sex		
Female	2303 (54.64)	9192 (54.66)
Male	1912 (45.36)	7624 (45.34)
Age (SD)	42.82 (24.17)	42.82 (24.17)
Length of MSP coverage		
12 months or less	199 (4.72)	773 (4.60)
13 to 24 months	244 (5.79)	957 (5.69)
25 months or more	3772 (89.49)	15,086 (89.71)
Income Quintile		
1	699 (16.58)	3294 (19.59)
2	711 (16.87)	3483 (20.71)
3	809 (19.19)	3311 (19.69)
4	844 (20.02)	3214 (19.11)
5	1104 (26.19)	3269 (19.44)
Missing	48 (1.14)	245 (1.46)
IBS prior to exposure		
Yes	106 (2.51)	Too few
No	4109 (97.49)	cases
CCI		
0	3388 (80.38)	14,884 (88.51)
1 to 2	668 (15.85)	1720 (10.23)
3 or more	159 (3.77)	212 (1.26)
Antibiotic exposure		
Yes	368 (8.73)	564 (3.35)
No	3847 (91.27)	16,252 (96.65)
PPI exposure		
Yes	573 (13.59)	657 (3.91)
No	3642 (86.41)	16,159 (96.09)
Statins exposure		
Yes	363 (8.61)	1329 (7.90)
No	3852 (91.39)	15,487 (92.10)
Immunosuppressive exposure		
Yes	32 (0.76)	59 (0.35)
No	4183 (99.24)	16,757 (99.65)
Immunomodulatory exposure		
Yes	144 (3.42)	282 (1.68)
No	4071 (96.58)	16,534 (98.32)

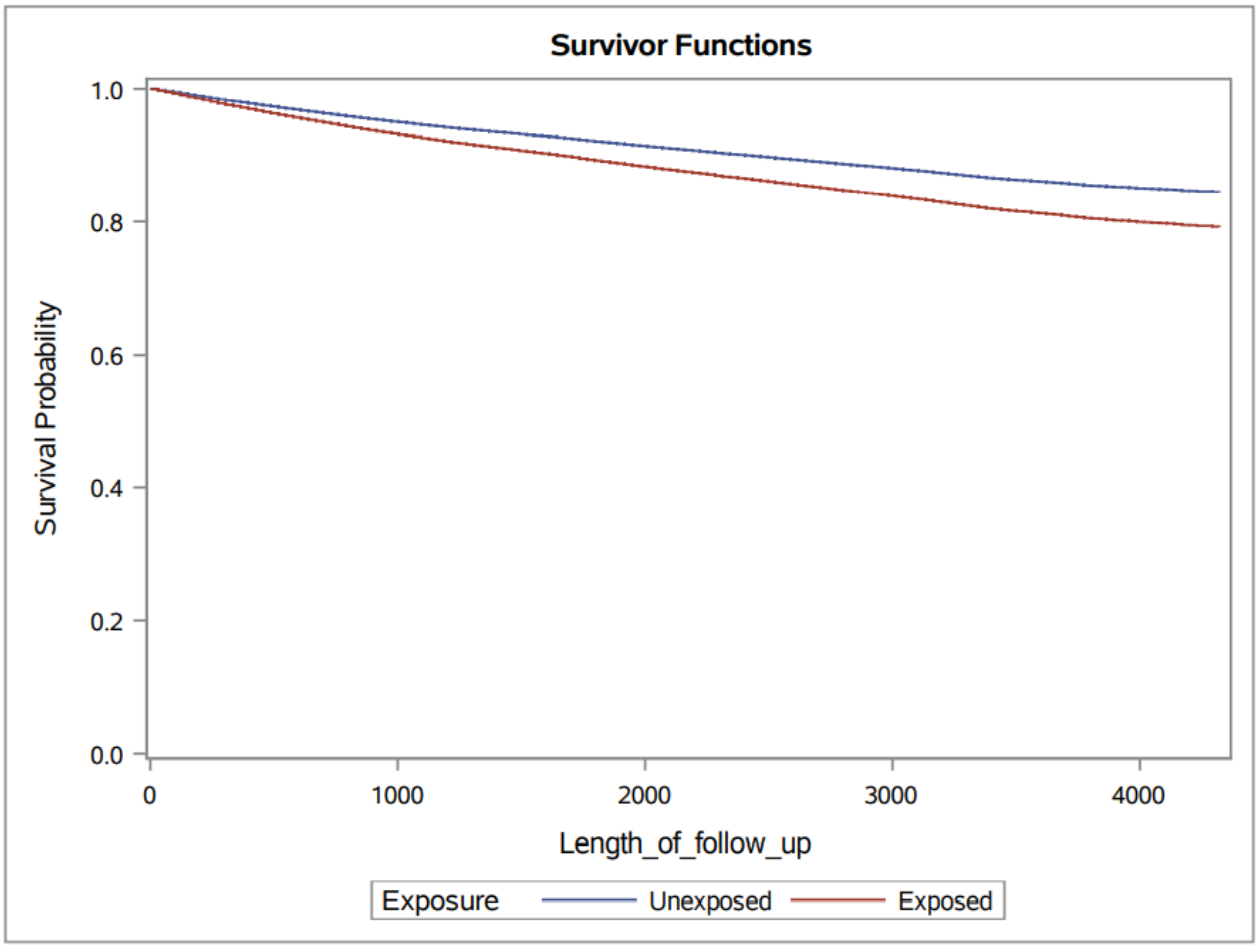
Table 4 - HR for DD in individuals exposed to FBI compared to non-exposed, with 95% CI

	Frequencies		HR [95% CI]	
	No. of patients (%)	**No. of cases of DD (%)**	**Crude**	**Adjusted***
Main analysis - exposed once, one pathogen				
No FBI	133,068 (79.96)	12,273 (9.22)	1.00 [ref.]	1.00 [ref.]
Any FBI	33,360 (20.04)	4515 (13.53)	1.49 [1.44; 1.55]	1.38 [1.33; 1.43]
Sensitivity analysis - including coinfected				
No FBI	135,877 (79,95)	12,502 (9.20)	1.00 [ref.]	1.00 [ref.]
Any FBI incl. coinfected	34,066 (20,05)	4643 (13.63)	1.51 [1.46; 1.56]	1.39 [1.34; 1.44]
Sensitivity analysis - including coinfected and repeateadly infected				
No FBI	143,606 (79.95)	13,183 (9.18)	1.00 [ref.]	1.00 [ref.]
Any FBI incl. coinfected & repeatedly	36,003 (20,05)	4784 (13,29)	1.51 [1.46; 1.56]	1.39 [1.34; 1.44]
Individual pathogen				
Campylobacter - Unexposed matches	52,625 (31.62)	4942 (9.39)	1.00 [ref.]	1.00 [ref.]
Campylobacter - Exposed patients	13,184 (7.92)	1800 (13.65)	1.48 [1.40; 1.56]	1,36 [1.28; 1.44]
Salmonella non-typhi - Unexposed matches	26,802 (16.10)	2221 (8.29)	1.00 [ref.]	1.00 [ref.]
Salmonella non-typhi - Exposed patients	6714 (4.03)	816 (12.15)	1.50 [1.38; 1.62]	1.40 [1.29; 1.52]
Giardia - Unexposed matches	18,453 (11.09)	1631 (8.84)	1.00 [ref.]	1.00 [ref.]
Giardia - Exposed patients	4644 (2.79)	578 (12.45)	1.42 [1.29; 1.56]	1.34 [1.21; 1.48]
Yersinia - Unexposed matches	16,816 (10.10)	1772 (10.54)	1.00 [ref.]	1.00 [ref.]
Yersinia - Exposed patients	4215 (2.53)	726 (17.22)	1.70 [1.56; 1.85]	1.58 [1.44; 1.74]
Shigella - Unexposed matches	4927 (2.96)	505 (10.25)	1.00 [ref.]	1.00 [ref.]
Shigella - Exposed patients	1236 (0.74)	218 (17.64)	1.76 [1.50; 2.06]	1.55 [1.30; 1.85]
STEC - Unexposed matches	4468 (2.68)	405 (9.06)	1.00 [ref.]	1.00 [ref.]
STEC - Exposed patients	1119 (0.67)	122 (10.90)	1.21 [0,99; 1.48]	1.15 [0.93; 1.42]
Exposure to antibiotics				
Yes				
No FBI	4204 (2.53)	565 (13.44)	1.00 [ref.]	1.00 [ref.]
Any FBI	2966 (1.78)	484 (16.32)	1.22 [1.08; 1.37]	1.14 [1,01; 1.28]
No				
No FBI	128,864 (77.43)	11,708 (9.09)	1.00 [ref.]	1.00 [ref.]
Any FBI	30,394 (18.26)	4031 (13.26)	1.48 [1.43; 1.54]	1.40 [1.35; 1.46]

		Frequencies		HR [95% CI]	
		No. of patients (%)	**No. of cases of DD (%)**	**Crude**	**Adjusted***
IBS prior to FBI					
	Yes				
	No FBI	26 (0.02)	Too few cases	1.00 [ref.]	1.00 [ref.]
	Any FBI	590 (0.35)	133 (22.54)	1.49 [0.55; 4.02]	1.30 [0.48; 3.51]
	No				
	No FBI	133042 (79.94)	12,269 (9.22)	1.00 [ref.]	1.00 [ref.]
	Any FBI	32,770 (19.69)	4382 (13.37)	1.47 [1.42; 1.52]	1.36 [1.32; 1.41]
Sex					
	Female				
	No FBI	61,913 (37.20)	7213 (11.65)	1.00 [ref.]	1.00 [ref.]
	Any FBI	15,526 (9.33)	2602 (16.76)	1.48 [1.41; 1.54]	1.37 [1.31; 1.43]
	Male				
	No FBI	71,155 (42.75)	5060 (7.11)	1.00 [ref.]	1.00 [ref.]
	Any FBI	17,834 (10.72)	1913 (10.73)	1.53 [1.45; 1.61]	1.41 [1.33; 1.48]

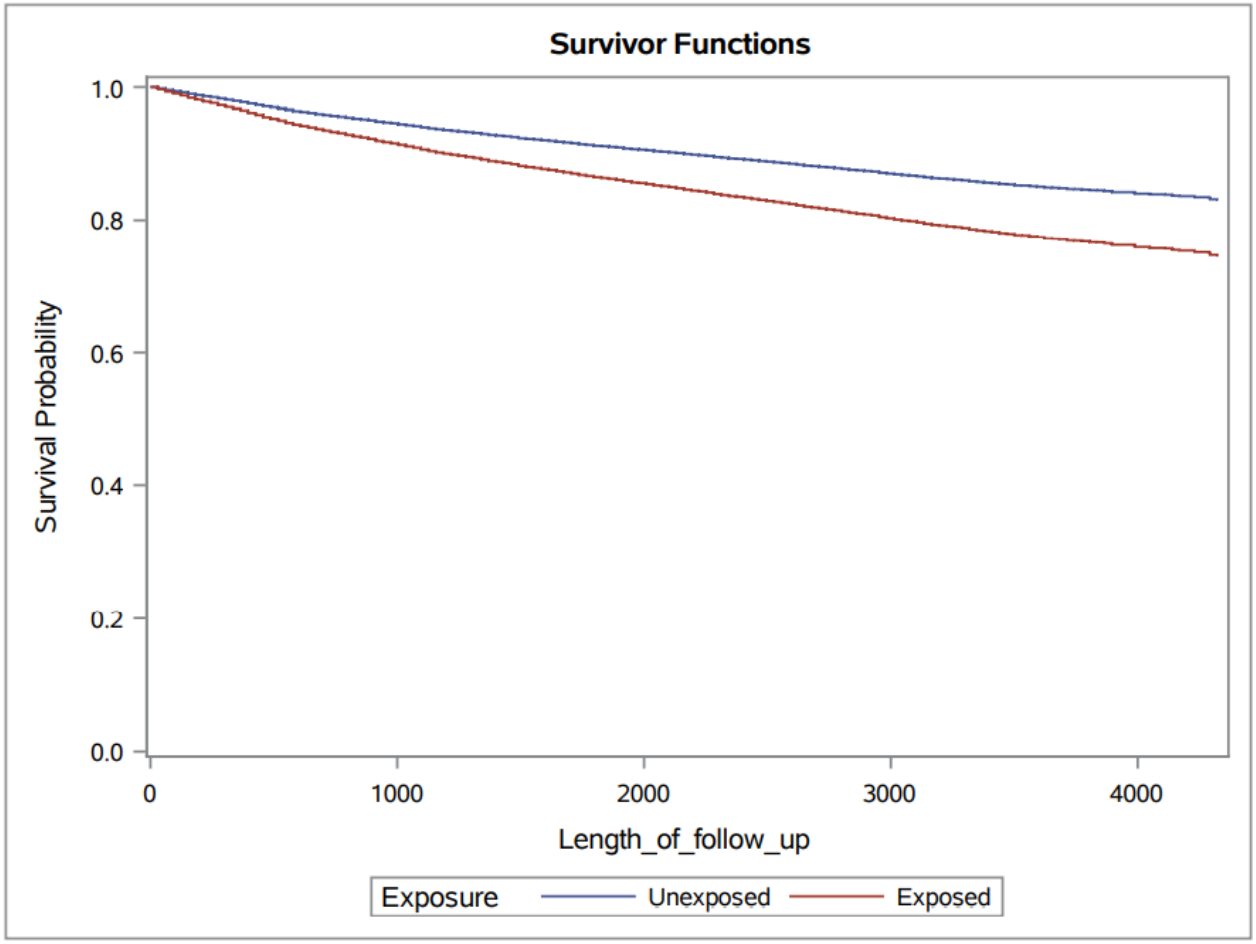
* Includes the propensity score (PS) as an adjustment variable. The PS takes into account age, sex, income decile, LHA, recent exposure to antibiotics, PPIs, statins, immunosuppressive agents, immunomodulatory agents and CCI

Figure 1 - Survivor functions of depressive disorders comparing individuals with laboratory-confirmed exposure to foodborne illnesses to individuals without confirmed exposure



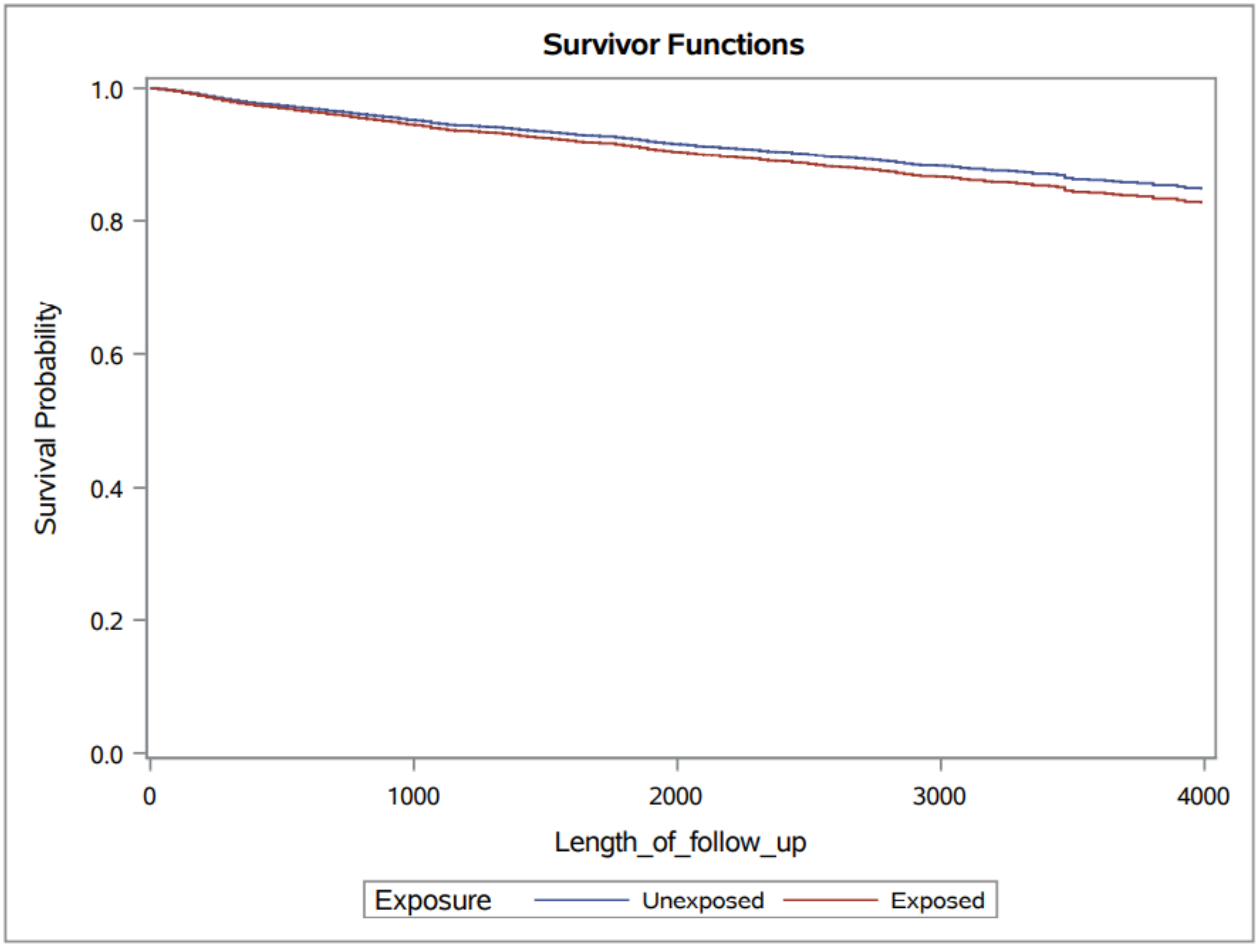
*Length of follow-up is measured in days

Figure 2 - Survivor functions of depressive disorders comparing individuals with laboratory-confirmed exposure to Yersinia to individuals without confirmed exposure



*Length of follow-up is measured in days

Figure 3 - Survivor functions of depressive disorders comparing individuals with laboratory-confirmed exposure to Shiga Toxin–Producing Escherichia Coli to individuals without confirmed exposure



*Length of follow-up is measured in days

Supplemental Table 1 - List of medications considered to determine exposure to antibiotics, proton-pump inhibitors, statins, immunosuppressant and immunomodulatory agents

Included			Excluded DINs
	AHFS class	**Product**	
Antibiotics	**8:12.02 Aminoglycosides**	Amikacin	
		Gentamicin	02238818*, 02023776*, 02023822*, 02219581*, 02212927*, 02148404*, 00832162*, 01989073*, 00872873*, 00872881*, 02237689*, 02230889*, 00776521*, 02238819*, 00805025*, 00805386*, 02229440*, 02229441*, 02230888*
		Streptomycin	02305577^
		Tobramycin	02245698*, 02239577*, 02241755*, 02389622°, 02443368°, 02457563°, 02239148*
	8:12.06.04 First Generation Cephalosporins	Cefadroxil	
		ceFAZolin	
		Cephalexin	
	8:12.06.08 Second Generation Cephalosporins	Cefaclor	
		Cefprozil	
		Cefuroxime	
		cefOXitin	
	8:12.06.12 Third Generation Cephalosporins	Cefixime	
		Cefotaxime	
		cefTAZidime	
		Tazobactam	
		cefTRIAXone	
	8:12.06.16 Fourth Generation Cephalosporins	Cefepime	
	8:12.06.20 Fifth Generation Cephalosporins	Ceftobiprole	
	8:12.07.08 Carbapenems	Doripenem	
		Ertapenem	

	Imipenem and Cilastatin	
	Meropenem	
8:12.07.12 Cephamycins	cefOXitin	
8:12.12.92 Other Macrolides	Azithromycin	
	Clarithromycin	
8:12.16.04 Natural Penicillins	Penicillins	00224359^, 00695181^, 02174626^, 02139219^, 02371227^, 00295736^, 01989944^, 02300745^, 01937995^, 00157872^, 00051942^, 00327050^, 00491020^, 00345466^
8:12.16.08 Aminopenicillins	Amoxicillin	02447584^, 00795925^, 02184613^, 00574910^, 00632635^
	Clavulanate	
	Ampicillin	
8:12.16.12 Penicillinase-resistant Penicillins	Oxacillin	
8:12.16.16 Extended-spectrum Penicillins	Piperacillin	
8:12.18 Quinolones	Ciprofloxacin	02253933*, 02387131*, 02506882*, 02481901*
	levoFLOXacin	
	Moxifloxacin	02404656*, 02484757*, 02406373*, 02472120*, 02485702*, 02429578*, 02432218*, 02411520*, 02420511*
	Ofloxacin	02248398*
	Norfloxacin	01908294*
8:12.20 Sulfonamides	sulfADIAZINE	02170310*, 01913115*
	Co-trimoxazole (**search as sufamethoxazole)	
8:12.24 Tetracyclines	Doxycycline	
	Minocycline	

		Tetracycline	02370263^, 00283851^, 00587427^, 00560197^, 00560200^, 00654787^, 00449989^, 02184591^, 00449989^, 00719315^, 00587435^, 00637513^, 02256983^, 00418323^, 00571350^, 00666254^, 00643165^, 02316064^, 00702587^, 02458322^, 00792594*, 02257009^, 02281058^, 00619426^, 00527777^, 01941208^, 02256991^, 02299666^, 02303566^, 00308153^, 00236594^, 00236365^, 02087219^
	8:12.24.12 Glycylcyclines	Tigecycline	
	8:12.28.08 Bacitracins	Bacitracin	02369214*, 02408317^, 02512866^, 02451026*, 02060833*, 00012351*, 02374390*, 02481812*, 02333562*, 02351714*, 02094754*, 00824186^, 00875864^
	8:12.28.12 Cyclic Lipopeptides	DAPTOmycin	
	8:12.28.16 Glycopeptides	Vancomycin	02420295~, 02420309~, 02420317~, 02420325~, 02406535~, 0002406543~, 02406551~, 02406578~, 02241821~, 02241820~, 01990888~, 001990861~, 01990853~, 00015423~, 00722146~, 02396386~, 02411032~, 02411040~, 02342855~, 02342863~, 02405822~, 02405830~, 02435713~, 02435721~, 02015110~, 02139243~, 02139375~, 02139383~, 02230191~, 02230192~, 02241807~, 02378337~, 02378345~, 02394626~, 02394634~, 02394642~, 02394650~, 02407914~, 02407922~, 02407930~, 02407949~, 02477793~, 02477807~, 02477815~, 02502593~, 02502607~, 02487071~, 02487063~
	8:12.28.20 Lincomycins	Clindamycin	02483769*, 02245830^, 02245831^, 02245832^, 02464519*, 02266938*, 02440180*
	8:12.28.24 Oxazolidinones	Linezolid	

	8:36.00 Urinary Anti-Infectives	Trimethoprim	01905031^, 00555657^, 02285495^, 01923838^, 02240363*, 02011956*, 02240122^, 02239234*, 02503425^, 00667161^, 02146002^, 02146053^, 00667218^, 00667145^, 02146029^, 02146037^, 01934031^, 02146045^, 00667153^, 00667188^, 02146010^, 00667196^, 02146096^, 00667226^, 00667234^, 02146061^, 02184559^, 01950584^, 00667145^, 02146029^, 02146037^, 01934031^, 02146045^, 00667153^, 00667188^, 02146010^, 00667196^, 02146096^, 00667226^, 00667234^, 02146061^, 02184559^, 01950584^, 02145995^, 00663786^, 02320835^, 02241375^
Proton-pump Inhibitors	**56:28.36 Proton-pump Inhibitors**	Dexlansoprazole	
		Esomeprazole	
		Lansoprazole	
		Omeprazole	
		Pantoprazole	
		RABEprazole	
Statins	**24:06.08 HMG-CoA Reductase Inhibitors**	Atorvastatin	
		Fluvastatin	
		Lovastatin	
		Pravastatin	
		Rosuvastatin	
		Simvastatin	
Immunomodulatory Agents	**92:20 Immunomodulatory Agents**	Alemtuzumab	
		Dimethyl Fumarate	
		Glatiramer	
		Interferon Beta	
		Natalizumab	
		Ocrelizumab	
		Peginterferon Beta-1A	
		Teriflunomide	
		Thalidomide	
		Daclizumab	

		Fingolimod	
		Abatacept	
		Adalimumab	
		Aldesleukin	
		Anakinra	
		Apremilast	
		Auranofin	
		azaTHIOprine	
		Certolizumab	
		cycloSPORINE	
		Etanercept	
		Golimumab	
		Hydroxychloroquine	
		inFLIXimab	
		Interferon Alfa	
		Leflunomide	
		Lenalidomide	
		Methotrexate	
		Pomalidomide	
		sulfaSALAzine	
		Tocilizumab	
		Tofacitinib	
		Ustekinumab	
Immunosuppressant Agents	**92:44 Immunosuppressive Agents**	azaTHIOprine	
		cycloSPORINE	02462486*
		Mycophenolate	
		Sirolimus	
		Tacrolimus	
		Everolimus	
		Mercaptopurine	
		Methotrexate	
		Basiliximab	
		Belimumab	
		Alefacept	
		Cyclophosphamide	
	52:08.08 Corticosteroids	Beclomethasone	
		Budesonide	
		Dexamethasone	
		Fluticasone	
		Hydrocortisone	
		prednisoLONE	

		Triamcinolone	
		Betamethasone	
		Hydrocortisone	

Reason for exclusion:

*	Topical, ophthalmic or otic use so minimal systemic effects.
^	For veterinary use; not approved for human use.
~	Although used systemically, IV vancomycin has extremely poor penetration into the gut, and very little potential to affect gut microflora
°	Respiratory use (e.g. for cystic fibrosis). In general, inhaled tobramycin has low systemic absorption and so systemic side effects are rare

6. DISCUSSION

6.1 Summary of Findings

The aim of this thesis was to determine whether laboratory-confirmed exposure to an FBI increases the risk of a subsequent diagnosis of DD in the general population. This subject was investigated following the publication of a few studies without laboratory-confirmed pathogen identification indicating a link between GI infections and depressive symptoms as well as a small survey study on the physical and mental health of patients recovering from STEC O104 affirming that same link.

To the best of my knowledge, this thesis is the first study investigating the impact of laboratory-identified enteric pathogens on the risk of developing DD through secondary analysis of administrative health data. Using the data from six administrative databases and one surveillance database provided by Population Data BC and a matched cohort design, we found that individuals with a laboratory-confirmed case of FBI had a 38% increased risk of subsequent DD diagnosis. The increase in risk was similar for both males and females. In the individual pathogen analyses, campylobacter, non-typhoidal salmonella, giardia, yersinia and shigella were all significantly associated with subsequent DD. While a markedly higher hazard ratio was observed for both yersinia (adj. HR= 1.58, 95% CI 1.44–1.74) and shigella (adj. HR= 1.55, 95% CI 1.30–1.85), only yersinia was associated with a significantly higher risk of developing DD compared with all other pathogens. Due to its large confidence interval, shigella could not be proven to be statistically more likely than other pathogens to be associated with DD. As yersinia patients appear to have different baseline characteristics compared with other FBI patients, this stronger association between yersiniosis and DD could be due to unmeasured confounding. STEC had a much lower HR than other pathogens and was not significantly associated with a higher risk of developing DD. As all the pathogens analysed individually were gram-negative bacterium, with the exception of Giardia, it was not possible to determinate whether exposure to a gram-negative bacterium increases the risk of developing DD more than exposure to other types of foodborne pathogens.

Sex and IBS status prior to the FBI did not differentially impact the risk of developing DD following exposure. However, stratifying based on recent antibiotic exposure revealed a discrepancy between the antibiotic exposed and unexposed groups. The HR of developing DD

following FBI exposure among those who were recently on antibiotics is not as high as the HR among those not exposed to antibiotics. Thus, the exposed and unexposed patients who were recently on antibiotics appear to be more similar in their risk of developing DD than those who were not exposed to antibiotics.

6.2 Study Findings in Relation with Existing Literature & Knowledge

The conclusion that laboratory-confirmed exposure to FBIs increases the risk of a subsequent DD diagnosis is coherent with the results of previous studies, which observed a greater risk of depressive symptoms or emotional difficulties in patients with suspected exposure to GI infections [8-10], and the magnitude of effect observed is relatively similar (IRR of 1.50 vs 1.62 in a prior study) [8].

However, this study did not confirm the association between STEC and DD that was previously identified in the literature [9]. The discrepancy between the results of this thesis and those of the anterior study on that point could be due to the hospital setting in which the later was conducted or the fact that it focussed only on the STEC O104 strain, both of which could have influenced the participants' risk of developing DD.

Despite the established association between IBS and DD described in existing literature [7], having a prior diagnosis of IBS was not associated with a higher HR of developing DD. However, as we have very few cases of IBS in both the exposed group (590, point prevalence at the time of FBI= 17.69 per 1000) and especially in the unexposed group (26, point prevalence at the time of matching= 0.20 per 1000). As this situation might be attributable to underdiagnosis/underreporting of IBS by physicians [79], it might be advisable in further studies to expand the algorithm for identifying IBS in administrative data.

6.3 Study Contribution to the Body of Knowledge

This study makes a significant contribution to the body of knowledge as it is the first study to observe an increase in the risk of a depression diagnosis following exposure to many specific laboratory-identified pathogens, including campylobacter, non-typhoidal salmonella, giardia, yersinia and shigella. After extensive research, it also appears to be the only study on that subject that stratifies on sex, which contributes to making medical research more inclusive, as it confirms the association observed between FBIs and DD is equally valid for both men and women. Finally,

as many existing studies are hospital-based, the study in this thesis is indicating that the link between GI infections and depression might also valid in healthier populations that have not been hospitalized/treated in a hospital due to the infection.

6.4 Strengths and Limitations of the Study

Among the strengths of this study, the datasets used contain demographic and health care use information about the complete population of British Columbia, which helps to ensure external validity of the results. The length of the period covered and extensiveness of the dataset also allowed for the identification of enough FBI cases to perform individual analyses per pathogen and for the inclusion of several covariates in the calculation of the propensity score. Moreover, the algorithm chosen to detect DD has been validated using administrative health care data from British Columbia and Alberta, a measure that should confirm the sensitivity and specificity of the algorithm in our study. This algorithm indeed include all but one of the diagnosis codes included in the case definition proposed by the BCCDC for depression, which reinforces its validity.

As for the limitations, although relying on laboratory-confirmed cases of FBI increased the specificity of the study, it likely underestimated the overall exposure to FBI in the population. Based on the estimates found in the literature, it would be reasonable to expect only about 1/10 of the FBI cases are captured in the Panorama data [80], most likely the most severe ones and those of patients who already have frequent medical visits. Nevertheless, this misclassification of exposure would tend to bias the results towards the null, which does not threaten the validity of this study's conclusions.

Under ascertainment of outcome is also a probable limitation. Due to the stigma attached with DD and the lack of formation of general practitioners to recognize the symptoms of the different conditions included in the DD category [81], it is likely many cases are never formally diagnosed. Moreover, the algorithm used only has a sensitivity of 61.4%, which implies that more than a third of depression cases recorded in the patient charts are not identified by the algorithm [56]. Finally, the existence of code 50B, an MSP code specific to BC and used for anxiety/depression that was not included in the algorithm, might also add to the under ascertainment, as some cases that would fulfill the criteria for a DD have likely been billed to the MSP using that code and thus, were not detected in our study. However, code 50B was not added to the algorithm due to it non-specificity and because it is likely to also be used for more minor episodes [82] that do not necessarily fulfill

the criteria for a diagnosis of DD, which justified its exclusion to maintain the specificity of the algorithm. As those sources of under ascertainment of outcome are unlikely to be differential, they would bias the results toward the null and thus would not put the results into question.

Some limitations are also inherent to the methodology chosen. For one thing, the validity of the outcome model is dependent on both the model used to calculate the propensity score and the outcome model being correctly specified [83]. Also, as the only adjustment variable is the propensity score, which is calculated based on covariates at the time of exposure, physical sequelae that can develop after an FBI are not considered, even though they might influence the risk of developing DD. Conditions such as IBS and reactive arthritis, which are possible sequelae of yersiniosis as well as other FBIs [26], might influence the risk of developing DD [7, 84]. More research will be needed to identify whether physical sequelae have an impact on the risk of developing DD after an FBI and to test different model specifications.

6.5 Modifications to the Initial Methodology

The initial protocol planned on matching individual with laboratory-confirmed FBI exposure to their unexposed matches using propensity score matching. However, this method of matching proved to be impractical with the dataset at hand. Due to the fact that we have data for the full population of BC, there is a very large number of unexposed individuals available to be matched in the dataset compared with the number of exposed individuals (raw proportion of exposure = 0.00000025). When calculating the propensity score for the full population, extreme values of propensity score were obtained (0 or 1), due to the raw proportion of exposure being so low that it drove a hugely negative intercept in the propensity score regression model. This situation posed a risk for the validity of the matching, as large differences in the covariates could result in imperceptible differences in the propensity score due to the disproportionate impact of the intercept on the propensity score.

To ensure proper balance of the main demographic covariates in the exposed and unexposed groups, the methodology was adjusted to first match exposed individuals with their unexposed matches based on the variables that we deemed most critical; these were sex, exact age, month, year and length of uninterrupted MSP coverage prior to the matching. The propensity score was then calculated only for the matched cohort, which made the distribution of the propensity score less extreme, and used the score as an adjustment factor in the adjusted models (i.e. I performed

propensity score regression). Although this alteration in the methodology has made it harder to find matches for very old individuals or individuals with a short length of uninterrupted MSP coverage, at least 1 match was found for each exposed individual and only 222 (0,007%) exposed individuals had fewer than 4 matches.

7. CONCLUSION

Using administrative data from British Columbia, the study described in this thesis documented a statistically significant increase in the risk of developing DD following a laboratory-confirmed FBI exposure. This association was maintained both in the main analysis of all FBIs and in the pathogen-specific analyses. Thus, FBIs might be associated with mental health sequelae that were previously unsuspected.

If the association observed in this study was to be confirmed by further research, it would reinforce the need for stringent sanitation measures at every step of the food supply chain to ensure established pathogen control procedures, such as pasteurization, are properly carried out and to minimize the risk of cross-contamination between food products during preparation. Encouraging sustainable farming practices could also help reduce the frequency of FBIs, as the overcrowding of animals on industrial scale installations favorizes the transmission of pathogens between the animals. Finally, the study findings, if confirmed by further research, could justify the creation of specific food handling guidelines aiming to minimize the risk of FBI exposure for groups that are at higher risk of developing DD, with advice such as avoiding foods that carry a higher risk of containing foodborne pathogens and favoring oven/skillet cooking over microwaving.

While that study is an important steppingstone for future work on the mental health sequelae associated with foodborne illnesses, more research is needed to establish the biological mechanism through which FBIs might impact the risk of developing DD, as well as whether other mental health conditions could be associated to FBIs. The association between the development of DD following an FBI and the presence of chronic physical sequelae of the FBI, such as post-infectious IBS and reactive arthritis, should also be investigated. Finally, research based on surveys and collection of biological samples rather that administrative data could help to determine whether individual pathogens have a different biological impact on the risk of developing DD or if unmeasured confounding is causing the stronger association of some pathogens with DD.

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Figure 4 - Histogram of the propensity score distribution

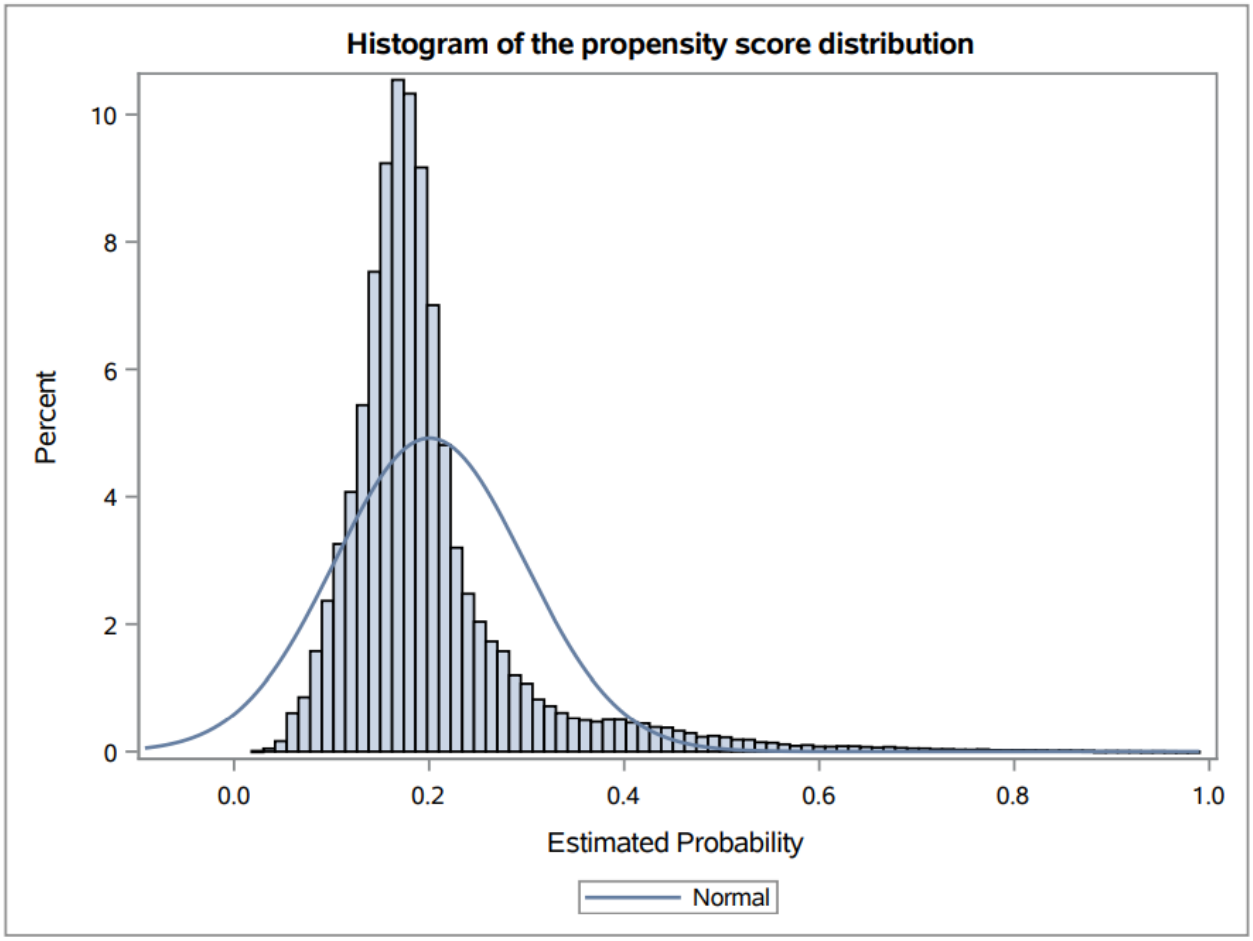

Figure 5 - Box plot of the propensity score distribution by exposure status