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The risk of new onset depression in association with influenza – A population-based observational study

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ABSTRACT

Importance: Case-reports provided evidence that influenza infections, particularly severe episodes, may exert neuronal damage in the CNS and thereby increase the risk of depression.
Objective: It was the aim of this study to analyse the association between influenza infections and the risk of developing incident depression.
Design: We conducted a case-control analysis between 2000 and 2013 using the large UK-based primary care database Clinical Practice Research Datalink (CPRD).
Setting: This database contains anonymous longitudinal data from primary care. At present, it contains over 100 million person-years of data from some 10 million active patients.
Participants: We encompassed 103 307 patients below the age of 80 years with an incident major depression diagnosis between 2000 and 2013, and matched each case to one control patient on age, sex, general practice, number of medical encounters, and years of history in the CPRD prior to the index date.
Exposure: Major depression diagnosis was identified by READ-codes based on ICD-10 codes (F32), with a minimum of three prescriptions for antidepressant drugs recorded after the diagnosis.
Main outcome: We calculated relative risk estimates of developing depression in association with previous influenza infections, stratified by the number, timing and severity of such events, and we adjusted for a variety of comorbidities, smoking status, alcohol intake, body mass index, use of oral corticosteroids, and benzodiazepines.
Results: Patients with a previous influenza infection had an increased risk of developing depression (OR 1.30, 95%CI 1.25–1.34) compared to patients with no history of influenza infections. A recent influenza infection recorded within 30–180 days prior to the index date yielded an adjusted 1.57 (95%CI 1.36–1.81), and an increasing number of previous influenza infections was associated with increasing odds ratios ($\geqslant$3 recorded influenza infections, adjusted OR 1.48, 95%CI 1.22–1.81).
Conclusion: This study suggests that influenza infections are associated with a moderately increased risk of developing depression.

1. Introduction

Unipolar depressive disorder is worldwide a common mental health problem (Thapar et al., 2012; Collins et al., 2011). The reported prevalence for major depression varies from 4.4% to approximately 20% (Bakish, 2001). The pathogenesis of the disease is not fully understood, and various causes including genetic risk factors have been discussed (Thapar et al., 2012). The research focus in depression has mainly been on the neurotransmitters noradrenalin and serotonin (Collins et al., 2011). However, cytokines and other immune transmitters may also contribute to depression in several ways. The «cytokine hypothesis» of depression, derived from both clinical and experimental observations, is supported by the finding that depressed individuals have been shown to have higher plasma levels of certain cytokines than healthy controls (Warner-Schmidt et al., 2011). Cytokines are part of the cell-to-cell communication in the immune system with pro- or anti-inflammatory properties. Further support of this hypothesis was also provided by clinical observations on patients treated with interferon (IFN) and interleukin-2 (IL-2) who

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displayed influenza-like symptoms and nonspecific neuropsychiatric symptoms including anorexia, fatigue, altered sleep patterns and pain, with a prevalence ranging from 0% to 45% (Baraldi et al., 2012; Pariante et al., 1999). In most cases, these symptoms could be successfully treated with antidepressants (Khairova et al., 2009).

Pro-inflammatory cytokines have been shown to be elevated in the blood during influenza infections (Toovey, 2008; Toovey et al., 2012). Interferon exerts antiviral activity by inhibiting protein synthesis and by limiting virus replication (Kreijtz et al., 2011). During severe influenza, hyper-induction of pro-inflammatory cytokine production has been shown to occur (Clark and Vissel, 2014; Darwish et al., 2011; Hui et al., 2013; Jang et al., 2012; Lee et al., 2011; Lee, 2009; To et al., 2010). Induction of pro-inflammatory cytokines by influenza vaccination has also been discussed (Segerstrom et al., 2012). Psychological distress seems to be associated with both poor antibody responses after vaccination and higher inflammatory markers, especially in older adults (Pedersen et al., 2009). We therefore explored in a large population-based observational study whether diagnosed influenza infections are associated with an altered risk of developing depression.

2. Methods

2.1. Data source

Data were derived from the UK-based Clinical Practice Research Datalink (CPRD), formerly known as the General Practice Research Database (GPRD). This database contains anonymous longitudinal data from primary care and was established around 1987. At present, it contains over 100 million person-years of data from some 10 million active patients (Cai et al., 2012). Individuals registered are representative of the UK population in terms of age, sex and geographical distribution. The CPRD has been validated extensively and proven to be of high data quality and completeness (Jick et al., 2003). The database had been used for previous epidemiological studies on depression (Schneider et al., 2010; Walters et al., 2011; Webb et al., 2012) and on influenza (Toovey et al., 2011; Meier et al., 2000). The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare Products Regulatory Agency (MHRA) database research.

2.2. Case and control selection

We identified in the CPRD all patients below the age of 80 years who had a first-time diagnosis of major depression between January 1, 2000 and the end of 2013. Cases were eligible if they had a minimum of three prescriptions for one or more antidepressant drugs recorded after the incident major depression diagnosis (i.e. the index date), identified by READ-codes based on ICD-10 codes (F32), if they started the antidepressant therapy within 90 days of the depression diagnosis, and if they have a minimum of three years of history before the incident depression diagnosis. In addition, cases were not allowed to have more than two prescriptions for antidepressants at any time prior to the index date. We introduced these steps to increase the likelihood of capturing confirmed depression diagnoses of clinically significant severity, and to increase the likelihood of identifying patients with an incident rather than a prevalent major depression diagnosis. We excluded all patients with a history of cancer, HIV-infection, or alcoholism. We identified at random one control patient per case from the base population, matched to cases on age (same year of birth), sex, general practice, calendar time (by using the same index date), and frequency of medical encounters at the general practice based on recorded diagnoses at different days in the year preceding the index date (<5, 5–19, $\geqslant$20 times). We matched on the number of medical encounters to account for possible detection bias, i.e. that patients with recent influenza were more likely to get depression diagnosed due to increased medical attention. We matched on general practice to make sure that cases and controls lived in the same geographical area and that they got the same type of medical attention. We selected controls at random from the CPRD population; they had to be free of a diagnosis of depression, or any antidepressant drug use at any time in their record. We applied the same exclusion criteria to the controls as we did to the cases.

2.3. Exposure

The exposure of interest was the presence of diagnosed and recorded influenza infections or influenza-like infections (ILI) prior to the index date. We quantified the number of such events, whereby multiple recordings had to be separated by at least 30 days in order to be counted as two independent infections. We further assessed the timing of the last influenza infection prior to the index date.

2.4. Analysis

We conducted conditional logistic regression analysis using the SAS statistical software version 9.4 (SAS Institute, Cary, NC) to calculate relative risk estimates of developing major depression in association with previous influenza infections with or without antibiotic use as odds ratios (ORs) with 95% confidence intervals (CI). We adjusted the analyses for a history of COPD, asthma, pneumonia, stroke, ischemic heart disease, myocardial infarction, sleep disorders, and affective disorders, which were all associated with an altered risk of depression in univariate analyses, and which can be associated with the likelihood of getting influenza, as well as for smoking status (non, current, ex, unknown), alcohol intake (non, current, ex, unknown) and body mass index (BMI; <25, 25–29.9, $\geqslant$30 kg/m^2).

Consistent with existing literature documenting a higher prevalence of depression in females (Essau et al., 2010; Rait et al., 2009), the majority of all depressed patients in our study were women (Table 1). In order to control for confounding by sex we matched cases and controls on sex. Of all cases, 28.8% were current smokers and 20.1% ex-smokers, proportions which were significantly higher than in controls (19.9% and 17.8% respectively; Table 1). Thus, current and ex-smokers were at higher risk of depression which is consistent with results of other studies which found that smoking is associated with an increased risk of major depression (Mineur and Picciotto, 2010; Glassman et al., 2001). Smoking may also be associated with stress and may have an effect on the hypothalamic pituitary adrenal (HPA) axis (Berlin, 2009; Richards et al., 2011). Cigarette smoking can be a confounder of the association of interest in this study since smoking is associated with depression (Baek et al., 2013) and with a possible increased susceptibility to influenza infection (Noah et al., 2012). Furthermore, smoking is associated with cardiovascular diseases, particularly with coronary heart disease (Dickens et al., 2012; Joynt et al., 2003), and cardiovascular diseases have also been linked to an altered risk of depression (Lippi et al., 2009). We tested these parameters in univariate analyses and found that they were associated with an increased risk of depression. In addition, the chronic pulmonary diseases COPD and asthma, which may predispose patients for influenza infections, were also associated with an increased risk of depression, as has been reported before (Jiang et al., 2014). We therefore adjusted the association of interest for these parameters. To address possible detection bias, we matched each patient not only on general practice, but also on the frequency of medical encounters in the