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Intestinal infection associated with future onset of an anxiety disorder: Results of a nationally representative study

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ABSTRACT

Recent research involving mice suggests a possible relationship between intestinal infection and future anxiety-like behavior. However, there has been little epidemiological research showing such a connection in humans. This study uses the Medical Expenditure Panel Survey (MEPS) to assess longitudinally the association between intestinal infection and later onset of an anxiety disorder, through a nationally representative sample. Six 2-year panel datasets, each comprised of 5 consecutive rounds, were pooled from 2007 to 2013 to gather records for all respondents 18 years of age or older that did not have an anxiety disorder in Round 1 ($n = 63,133$ people). Within the study sample, there were 2577 individuals with an intestinal infection in Round 1 and 4239 individuals with an anxiety disorder that began in Round 2, 3, 4, or 5. Overall, intestinal infection in Round 1 was associated with a 1.34 ($P < 0.01$) odds ratio of having an anxiety disorder that began in Round 2, 3, 4, or 5. Separate analyses were performed to determine whether the association applied to other infection types, including respiratory infection, urinary tract infection, hepatitis infection, and skin infection. Respiratory infection was associated with a 1.36 ($P < 0.01$) odds ratio of having an anxiety disorder that began in Round 2, 3, 4, or 5; no other infection type showed a significant association. More research on human populations is needed to examine the apparent association and explore potential mechanisms by which gut pathogens might influence anxiety.

1. Introduction

There has been a recent push to uncover the role intestinal pathogens might play in triggering anxiety disorders. Much of this research comes from exploring the gut-brain axis in studies assessing infectious bacterial activity in the intestines of mice. Mice infected with *Campylobacter jejuni* (*C. jejuni*), a food-born pathogen, exhibit greater activation in areas of the brain typically associated with anxiety (Goehler et al., 2008). Lyte et al. (2006) found similar links between infection in the gut and later anxiety-like behavior in mice. Mice that are given probiotics show reductions in anxiety-like behavior (Bercik et al., 2010; Messaoudi et al., 2011).

The exact mechanism by which infection in the gut might influence the brain is unclear. Several studies have shown that immune response might influence anxiety and mood (Maier and Watkins, 1998; Reichenberg et al., 2001; Pollak and Yirmiya, 2002). Through this path it is suggested that microbiota can influence behavior through a cytokine-mediated humoral route (Sudo et al., 2004). Dahlgren et al. (1995) found that interleukin-6 and Tumor Necrosis Factor (TNF) levels were elevated in mice following infection of *Escherichia coli*. Other studies have similarly found that intestinal infection raises immune response (Sudo et al., 2004; Lundin et al., 2008). However, Lyte et al. (2006) found mice exhibiting anxiety-like behavior following infection by *Citrobacter rodentium* even in the absence of circulating pro-inflammatory cytokine. The study found activation of vagal sensory neurons, suggesting that the connection between the gut and brain might not depend strictly on immune activation.

Other studies have also suggested that the vagus nerve plays a role in the gut-brain axis—specifically the role of vagal afferent neurons in transmitting information from the gut to the central nervous system (Goehler et al., 2005; Groves and Brown, 2005; Klarer et al., 2014). One possibility is that cytokines activate the vagal afferent fibers, which, in turn, send signals to the brain (Turnbull and Rivier, 1999).

The timeframe by which infection in the gut would influence anxiety-like behavior also remains unknown. Several studies suggest that the onset of anxiety can follow intestinal infection within a matter of hours (Goehler et al., 2005; Lyte et al., 2006; Goehler et al., 2008). Other studies suggest a much longer impact; two months after the eradication of *Helicobacter pylori* in infected mice, intestinal function had normalized, but abnormal eating behavior persisted, as did increased expression of TNF-αlpha

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(Bercik et al., 2009). Koloski et al. (2012) found that gastrointestinal disorders were associated with anxiety in a 12-year longitudinal study of a random population of approximately 1800 Australians. However, it is unclear whether the gastrointestinal disorders discussed in this study (Irritable Bowel Syndrome and functional dyspepsia) resulted from infection or from other means, making it difficult to draw conclusions about causation or timeframe.

While some large epidemiological studies have shown an association between infection and onset of psychiatric disorders (Goodwin, 2011; Benros et al., 2013), there has been comparatively little epidemiological research thus far on the role of infection in the gut in triggering anxiety disorders. This study aims to address that issue by using a nationally representative sample of Americans to assess whether intestinal infection is associated with later onset of an anxiety disorder. The study also examines the proximity between infection and onset of the disorder within a two-year span. In order to assess whether the association is limited to intestinal infection, other types of infections are considered as well.

2. Material and methods

2.1. Medical Expenditure Panel Survey

Data were taken from the Medical Expenditure Panel Survey (MEPS), a publically available health-related survey set representative of all civilian non-institutionalized Americans. MEPS includes information on households and individuals, medical conditions, services, and expenditures. Using computer-assisted personal interviewing (CAPI) technology to retrieve household member data, MEPS typically uses one adult in the household (i.e. the *household respondent)* to provide information on all household members.

MEPS uses a 2-year panel design segmented into 5 rounds, with Rounds 1 and 2 occurring in the first year and Rounds 4 and 5 occurring in the second year (Round 3 can overlap years). Longitudinal data on 6 MEPS panels were pooled: MEPS Panel 12 (2007–2008), 13 (2008–2009), 14 (2009–2010), 15 (2010–2011), 16 (2011–2012), and 17 (2012–2013). When pooled, the dataset offers records of 94,407 people; only people 18 or older who were alive throughout the survey and did not have an anxiety disorder in Round 1 of their panel were included in the study (63,133 participants who, when weighted for national estimates, represented 214,247,544 Americans).

A specific medical condition was identified for an individual if the household respondent identified a medical event (e.g. outpatient visit, prescribed medication purchase, or hospital stay), reported an individual taking disability days in response to a condition, or named any condition that negatively affected the individual. Professional coders then used the precise text recorded by interviewers to attach ICD-9-CM codes to the medical conditions. Codes were verified and did not exceed 2.5% error rate for any coder in any year. Clinical classifications software then aggregated specific ICD-9-CM codes into clinically meaningful condition codes referred to as CCCODEX codes. To preserve confidentiality, specific ICD-9-CM codes were collapsed from fully specified codes to 3-digit codes after being matched to CCCODEX codes. A detailed list of all specific ICD-9-CM codes matched to respective CCCODEX codes with data files can be found with the Agency for Healthcare Research and Quality (2016).

2.2. Measures

2.2.1. Anxiety disorder Round 1

A dummy variable for anxiety status was coded to reflect whether individuals reported a condition with a CCCODEX code of 651 beginning in Round 1 (*Anxiety Disorder*). This CCCODEX code encompassed all specific ICD-9-CM codes for anxiety disorders, including 300.01(*Panic Disorder without Agoraphobia*), 300.00 (*Generalized Anxiety Disorder*), and 300.3 (*Obsessive Compulsive Disorders*). This variable was used when restricting the population to include only those who did not have an anxiety disorder that began in Round 1. There were 3056 individuals who reported an anxiety disorder that began in Round 1.

2.2.2. Anxiety disorder Round 2, 3, 4, or 5

One dummy variable for anxiety status was coded to reflect whether individuals reported a condition with a CCCODEX code of 651 that began in Round 2, 3, 4 or 5. Four other dummy variables were coded to reflect the specific round in which the anxiety began.

2.2.3. Intestinal infection Round 1

A dummy variable for intestinal infection was coded to reflect whether individuals reported a condition with a CCCODEX code of 135 (*Intestinal infection*) in Round 1. The CCCODEX code encompassed all specific ICD-9-CM codes dealing with intestinal infection, such as ICD-9-CM code 008.02 (*Intestinal Infection Due to Enterotoxigenic E. coli*) and ICD-9-CM code 008.04 (*Intestinal Infection Due to Enterohemorrhagic E. coli*).

2.2.4. Other infections Round 1

A dummy variable for respiratory infection status was coded to reflect whether individuals reported a condition with a CCCODEX code of 122 (*Pneumonia, Except That Caused by Tub*), 123 (*Influenza*), 124 (*Acute and Chronic Bronchitis*), 125 (*Acute Bronchitis*), or 126 (*Other Respiratory Infections*) that began in Round 1. A dummy variable for skin infection was coded to reflect whether individuals reported a condition with a CCCODEX code of 197 (*Skin and Subcutaneous Tissue Infections*) that began in Round 1. A dummy variable for urinary tract infection was coded to reflect whether individuals reported a condition with a CCCODEX code of 159 (*Urinary Tract Infections*) that began in Round 1. A dummy variable for hepatitis infection was coded to reflect whether individuals reported a condition with a CCCODEX code of 006 (*Hepatitis*) that began in Round 1.

2.2.5. Demographics

Race, family income (Year 1), sex, years of education, and age were included as covariates in order to control for any major systematic demographic differences that might influence anxiety onset. Geographic location within America was also included as a covariate in order to control for any potential regional differences that might alter susceptibility to anxiety.

Information on whether respondents had an anxiety disorder or infection was found in the 2007–2013 Medial Conditions File. All other data came from the Panel 12–16 Longitudinal Data files (Agency for Healthcare Research and Quality, 2016).

2.3. Statistical analysis

2.3.1. Analysis 1 – anxiety onset followed by intestinal infection

Multiple logistic regression analysis with odds ratios was performed. Anxiety disorder status that began in Round 2, 3, 4, or 5 was the dichotomous, dependent variable. The regression adjusted for several covariates including family income (logged), geographic location, years of education, age, race, and sex. Family income, age, and education were all mean centered prior to entry into regression. The analysis adjusted for MEPS survey design in order to calculate unbiased variances for national estimates.