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Nitrated meat products are associated with suicide behavior in psychiatric patients

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ABSTRACT

There has been little previous study of the association between dietary factors and suicide. The association between food exposures and suicide attempt history was investigated in a sample of 270 individuals with schizophrenia, bipolar disorder, or major depressive disorder. Individuals who had a suicide attempt history were almost 3 times as likely to report eating cured meat, typically prepared with added nitrates, compared to patients without a suicide attempt history, adjusting for demographic and clinical variables. A suicide attempt history was 6 times greater in those who in addition were cigarette smokers and had a history of substance abuse compared to those who did not have any of these risk factors. If dietary factors were shown to affect suicide risk, an additional method of risk reduction would be available which could be widely disseminated to address this major public health problem.

1. Introduction

Suicide is a leading cause of death worldwide. In the United States more than 40,000 people die every year by their own hand (Centers for Disease Control, 2016). The causes of suicide are complex and not fully understood. One major risk factor that has been identified is the diagnosis of a serious psychiatric disorder. Psychological autopsy and epidemiological studies indicate that more than 90% of people who kill themselves have a diagnosable psychiatric illness, particularly major depression, bipolar disorder, or schizophrenia (Cavanagh et al., 2003; Nordentoft et al., 2011). Other clinical and environmental factors that have been shown to increase suicide risk are life adversity, personality characteristics such as impulsivity, and co-occurring substance use (Dumais et al., 2005; Foster et al., 1999; Nordentoft et al., 2011).

We recently examined the association between food exposures and diagnosis in a cohort of individuals with psychiatric disorders and controls without a psychiatric disorder. We found that a history of eating cured meat was significantly and independently associated with hospitalization for mania (Khambadkone et al., 2018). We also found some associations between a history of eating cured meat and other psychiatric disorders but the differences were not statistically significant. The association between the ingestion of cured meat products and altered behavior was substantiated by experimental animal studies in which laboratory rats were fed meat preparations with added nitrate, the main additive found in cured meat products. Rats who received these products displayed hyperactivity, changes in the intestinal microbiome and alterations in brain pathways that have been implicated in mood disorders and suicide behaviors.

We undertook the current study to determine if a history of eating nitrated meat was associated with a history of suicide behaviors in individuals with psychiatric disorders.

2. Methods

2.1. Sample

The study sample consisted of individuals with schizophrenia-spectrum disorders, bipolar disorder, and major depressive disorder who were recruited consecutively in the period May 1, 2014 through May 30, 2018. These individuals were enrolled in ongoing studies of the role of infections and the immune response in individuals with serious psychiatric disorders (Dickerson et al., 2016). The sample here represents a subset of the sample previously studied as to correlates of dietary exposure(Khambadkone et al., 2018) and includes all of the participants since an assessment of suicide attempt history was added to the study procedures.

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The inclusion criterion for individuals with schizophrenia-spectrum disorder was a current diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, or psychotic disorder not otherwise specified. The inclusion criterion for individuals with bipolar disorder was a diagnosis of bipolar disorder including bipolar I disorder, bipolar II disorder, or bipolar disorder not otherwise specified, and for major depressive disorder, single or recurrent major depression. Participants were recruited from inpatient, day hospital, and rehabilitation programs of Sheppard Pratt Health System and from affiliated psychiatric agencies. The diagnosis of each psychiatric participant was established by the research team including a board-certified psychiatrist and based on the Structured Clinical Interview for DSM-IV Axis 1 Disorders (First et al., 1996) and available medical records.

Participants met the following additional criteria: age 18–65; proficient in English; absence of any history of intravenous substance abuse; absence of mental retardation; absence of HIV infection; absence of serious medical disorder that would affect cognitive functioning; absence of a primary diagnosis of alcohol or substance use disorder over the past 3 months.

The studies were approved by the Institutional Review Boards of the Sheppard Pratt Health System and the Johns Hopkins Medical Institutions following established guidelines to protect participants based on the Declaration of Helsinki. All participants provided written informed consent after the study procedures were explained.

2.2. Food exposures

Food exposures were assessed by a questionnaire developed and administered by research staff and adapted from one developed to assess for sources of exposure to infection with *Toxoplasma gondii* (Cook et al., 2000). This questionnaire asked the participants to indicate whether or not they had eaten certain types of food. Data were not collected regarding the amount of food consumed or the timing of consumption. Questions addressed to the participants included *"Have you ever eaten dry cured meat such as beef jerky, meat sticks, or Turkey jerky"? "Have you ever eaten undercooked fish such as rare tuna?"*; *"Have you ever eaten raw fish such as sushi or sashimi?"* and "*Have you ever eaten undercooked meat?"*

2.3. Measure of suicide attempts

All participants were assessed by trained raters on the Columbia Suicide Severity Rating Scale (Posner et al., 2011) about suicide behaviors including the history of an actual suicide attempt, an interrupted attempt, or an aborted attempt during the lifetime. A suicide attempt was defined as a potentially self-injurious act committed with at least some wish to die as a result of the act; an interrupted attempt when a person is interrupted (by an outside circumstance) from starting the potentially self-injurious act and, if not for that, the actual attempt would have occurred; an aborted attempt when a person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior

2.4. Clinical assessments

Participants were also interviewed and rated on the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) and were evaluated on a cognitive battery, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998). Participants were interviewed about their recent and past use of alcohol and drugs and classified in one of three groups: no history, past history only, or recent history in the last 3 months. Participants were asked about demographic variables including maternal education as a proxy for pre-morbid socioeconomic status and their current cigarette smoking status. Body mass index (BMI) was calculated based on height and weight measured by research staff.

Current medications received were recorded from clinical charts and participant self-report and it was noted whether each patient was receiving the following types of medication at the time of the study visit: atypical anti-psychotic, lithium, valproate, antidepressant medication.

2.5. Statistical analysis

Bivariate associations between suicide attempt history and demographic, clinical, and dietary variables were assessed by chi-square analysis for categorical variables and analysis of variance for continuous variables. The relationship between suicide attempt history and clinical and dietary variables was further determined through the use of a multivariate logistic regression model; included in the model were clinical and dietary variables that had some association with suicide history in the bivariate analyses ($p < .1$). The relationship between suicide attempt history and clinical and dietary variables was further studied in a multivariate logistic model that included different combinations of risk factors to predict suicide attempt history and also the other clinical variables associated with suicide attempt history. The regression models controlled for the demographic variables age, sex, race, and maternal education as a proxy for premorbid socioeconomic status; in 7 cases where maternal education was not available, paternal education was substituted.

These statistical analyses were performed by the use of STATA v15 (Stata Corporation, College Station, TX).

3. Results

The sample consisted of $N = 270$ persons with a diagnosis of schizophrenia ($n = 122$), bipolar disorder ($n = 87$) or major depressive disorder ($n = 61$) drawn from a psychiatric health system; a total of 161 (60%) were ascertained when they were inpatients. A total of 156 (58%) of participants had a history of a suicide attempt. Among this group, there were 122 actual suicide attempts, 69 aborted attempts, and 39 interrupted attempts.

The characteristics of study participants are shown in Table 1, as well as the bivariate associations between suicide attempt history and demographic, clinical variables, and dietary variables. A suicide attempt history was significantly associated with being a cigarette smoker ($chi^2 = 5.46$, $p = .019$), a history of substance abuse ($chi^2 = 9.86$, $p = .002$), the report of eating cured meat ($chi^2 = 8.42$, $p = .004$), and marginally associated with receipt of an antidepressant medication ($chi^2 = 3.21$, $p = .073$). Suicide attempt history was inversely associated with being foreign-born ($chi^2 = 5.53$, $p = .019$). In a multivariate logistic regression on suicide attempt history, a history of eating cured meat remained significant in the model (OR = 2.89, 95% CI 1.13, 7.22, $p = .025$). Also significant in the model was foreign birth (OR = 0.24, 95% CI 0.06, 0.95, $p = .042$), indicating that foreign birth was associated with a reduced risk.

In the multiple logistic regression on suicide attempt history including combinations of risk factors (eating cured meat, history of substance abuse, cigarette smoker), the OR was 6.01 (95% CI 1.47, 24.6, $p = .013$) for those who had all 3 risk factors. There were also significantly increased odds for the combination of eating cured meat, positive substance abuse history, and no current cigarette smoking: OR = 4.26 (95% CI 1.05, 17.32, $p = .043$). Foreign birth also remained significant in both of these models, indicating a lower risk for a history of a suicide attempt associated with being foreign born. A history of a suicide attempt was not associated with other food-based exposures such as eating raw meat, raw fish, undercooked meat or undercooked fish. Neither a history of a suicide attempt or eating cured meat was associated with symptom severity as measured by the BPRS, cognitive functioning as measured by the RBANS, or other clinical or demographic variables (all $p > .05$).

Table 1
Participant characteristics by suicide attempt history.

	History of suicide attempt (n = 156)	No history of suicide attempt (n = 114)	Total sample (N = 270)
Age[1]	37.3 (± 13.1)	40.0 (± 13.3)	36.3 (± 13.2)
Sex, male	79 (51%)	66 (58%)	145 (54%)
Race, Caucasian	89 (57%)	65 (57%)	154 (57%)
Birth outside of US or Canada[2]	3 (2%)	9 (8%)	12 (4%)
Marital Status			
-Single never married	107 (69%)	87 (76%)	194 (72%)
-Married	17 (11%)	14 (12%)	31 (11%)
-Divorced/separated	31 (20%)	13 (11%)	44 (16%)
-Widowed	1 (1%)	0 (0%)	1 (<1%)
Maternal Education	13.1 (± 3.0)	13.7 (± 3.0)	13.4 (± 3.0)
Cigarette Smoker[3]	77 (49%)	40 (35%)	117 (43%)
Body Mass Index	31.7 (± 8.5)	30.4 (± 8.4)	31.1 (± 8.5)
Schizophrenia vs. Affective disorder diagnosis	72 (46%)	50 (44%)	122 (45%)
History of substance abuse (past or recent)[4]	139 (89%)	85 (75%)	224 (83%)
Care setting			
-Inpatient	78 (50%)	52 (45%)	130 (48%)
-Day hospital	14 (9%)	17 (159%)	31 (11%)
-Outpatient	64 (41%)	45 (39%)	109 (40%)
BPRS[5] score	50.1 (± 8.2)	48.3 (± 8.9)	49.3 (± 8.5)
RBANS[6] total cognitive score	70.5 (± 14.4)	71.2 (± 13.2)	70.8 (± 13.9)
Medication			
-Atypical antipsychotic	106 (68%)	75 (66%)	181 (67%)
-Lithium	25 (16%)	27 (24%)	52 (19%)
-Valproate	39 (25%)	26 (22%)	65 (24%)
-Antidepressant[7]	87 (56%)	51 (45%)	138 (51%)
Dietary variables, report of eating			
Cured meat[8]	147 (94%)	95 (83%)	242 (90%)
Undercooked meat	126 (81%)	83 (73%)	209 (77%)
Undercooked fish	97 (62%)	74 (65%)	171 (63%)
Raw meat	33 (21%)	24 (21%)	57 (21%)
Raw fish	90 (58%)	71 (62%)	161 (60%)

[1] Values represent mean (sd) or number (percent).
[2] Between group differences, $chi^2 = 5.53$, $p = .019$.
[3] Between group differences, $chi^2 = 5.46$, $p = .019$.
[4] Between group differences, $chi^2 = 9.86$, $p = .002$.
[5] BPRS, Brief Psychiatric Rating Scale.
[6] RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.
[7] Between group differences, $chi^2 = 3.21$, $p = .073$.
[8] Between group differences, $chi^2 = 8.42$, $p = .004$.

4. Discussion

We found that a history of eating cured meat was associated with increased odds of having a history of a suicide attempt. The exact mechanism by which a history of eating cured meat might be linked with suicide attempts is not known with certainty. However it is of note that rats fed meat with added nitrates, the main additive of cured meat preparations, displayed changes in behavior and alterations in brain pathways, some of which have been associated with suicide in humans (Khambadkone et al., 2018). Of particular interest is the serotonin pathway which was altered in the rats fed meat with added nitrate and which has been linked to suicide and suicide attempts based on both genetic susceptibility and alteration in levels of reactants within the brain (Sullivan et al., 2015).

Only a few studies have examined the association between dietary exposures and suicide behavior. A large population-based study in Japan found that a "prudent diet" characterized by a high intake of vegetables, fruits, potatoes, soy products, mushrooms, seaweed and fish was associated with a reduced risk of death by suicide (Nanri et al., 2013). However, a small case control study in Canada did not find an association between a suicide attempt history and diet based on reported intake of fish and seafood, nuts, fruits, and vegetables (Perera et al., 2018). Data from the US NHANES survey showed that patients with low intakes of polyunsaturated fat and fiber were more likely to have a history of a suicide attempt but specific foods were not identified as risk factors (Zhang et al., 2005).

Our finding about the inverse association between foreign birth and suicide attempt history is consistent with some studies indicating lower rates of suicide in US immigrant groups (Nasseri and Moulton, 2011; Singh and Miller, 2004) but not other studies which found an increased risk (Jones et al., 2016; Nasseri, 2008); variable results among studies are likely due to differences among immigrant groups, cohorts, and other determinants of suicidal behavior. The number of foreign-born persons in our sample was too small to analyze the results in more detail. The other variables that we found to be associated with suicidal behavior, cigarette smoking and substance abuse, have been well established in the literature as risk factors (Evins et al., 2017; Steele et al., 2018).

Our study had a number of limitations. We did not assess all of the clinical factors which may increase the risk for suicide, such as life adversity. While our assessment of suicide behavior used a standard rating scale, we did not collect data systematically about the timing of suicide attempts in relation to the intake of cured meat products nor did we study individuals who had made a recent suicide attempt, nor were we able to study suicide attempt lethality. We also do not know the source of the cured meat that participants reported eating nor the timing or dose of exposure. In addition, because of the relatively small sample size, our study was not adequately powered to study the added effect of blood-based markers (Dickerson et al., 2017).

A strength of our study was that we measured other dietary exposures in addition to cured meat such as eating raw meat and raw fish; cured meat was the only dietary exposure about which we inquired that was linked to suicide behavior, adding some specificity to our finding. However, there was a high exposure to cured meat reported by both those who did and who did not have a suicide attempt history, indicating that this exposure likely interacts with other factors to increase suicide risk.

We note that our study is among the first to assess dietary factors that are associated with suicide attempts, a topic which merits further investigation. Suicide, for which a previous suicide attempt is the greatest risk factor, is a major cause of death worldwide and is highly prevalent in patients with serious mental illness. Unfortunately, the ability to prevent suicide remains limited despite concerted and multifaceted efforts to do so (Zalsman et al., 2016). If dietary factors were shown to affect suicide risk, an additional method would be available which could be widely disseminated to address this major public health problem.

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