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Inflammation as a unique marker of suicide ideation distinct from depression syndrome among U.S. adults

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Abstract

Background: Recent evidence suggests that pro-inflammatory states may be independently associated with the risk of suicidality, above and beyond depression. This study assesses whether four indicators of inflammation, circulating levels of C-reactive protein (CRP), white blood cell (WBC) count and immunoglobulin E (IgE), and dietary inflammatory potential, measured using the Dietary Inflammatory Index® (DII), distinguish suicidal ideation (SI) from major depression (MD).

Methods: Data come from multiple cycles of the US National Health and Nutrition Examination Survey ($N_{\text{CRP}\&\text{WBC}} = 13,912$; $N_{\text{DII}} = 17,076$; $N_{\text{IgE}} = 4,060$). MD was measured using the Patient Health Questionnaire-9 (PHQ-9); SI was indicated by the last item of the PHQ-9. To assess SI independent from MD, participants were classified into four categories: SI with MD, SI without MD, MD without SI, and neither MD nor SI. Regression models were used to assess the relationship between indicators of inflammation and SI with and without MD. Results: None of the inflammatory indicators were able to distinguish SI status among MD cases. DII was associated with SI among individuals without MD. CRP, DII, and WBC were associated with MD. No associations were found for IgE.

Limitations: Cross-section data prevent drawing causal conclusions. Underreporting of MD and suicidal ideation and measurement of habitual diet using 24 h dietary recalls are also weaknesses.

Conclusion: Dietary inflammatory potential was associated with suicide ideation among US adults with and without depression. Diet may play a role in suicide ideation and more empirical evidence is needed to determine whether nutritional protocols could aid in the treatment of suicidal behaviors. Findings did not support inflammatory factors having a relationship with suicide ideation distinct from depression.

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Contributors

BM conceived of the study. RSB and KMK conduct analyses. RSB wrote the initial manuscript draft. All authors contributed to study design, interpretation of results and revision of the final manuscript.

Conflicts of interest

The authors report no biomedical financial interests or potential conflicts of interest.

Supplementary materials

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Keywords

Depression; Suicide; Leukocytes; Diet; Allergies; Inflammation

1. Introduction

Suicide is the 10th leading cause of death in the United States, and incidence has increased over the past 15 years. Suicidal ideation is relatively common, with 4% of adults in the general population reporting suicidal thoughts in the past year (Piscopo et al., 2016). While mood disorders such as major depression (MD) are established risk factors for suicide-related behavior, suicidal ideation and other behaviors (e.g. planning, attempts) also occur outside the context of depression (Miret et al., 2013) suggesting that a unique mechanisms or processes that may distinguish suicidal ideation from other symptoms of depression.

Activation of inflammatory pathways and MD onset has been replicated in several observational (Berk et al., 2011; Miller et al., 2009) and experimental studies, (Dowlati et al., 2010; Ohgi et al., 2013). However, fewer studies have examined links between inflammatory pathways and suicidal ideation. Prior research suggests an association between neuroinflammation, as measured by microglia activity in the brain, and suicidal thoughts when compared to healthy controls (Setiawan et al., 2015). Other evidence indicates that the kynurenine pathway, which is part of monoamine metabolism and affects glutamate neurotransmission, is a unique mechanism linking inflammation to suicide, distinct from depression (Brundin et al., 2015). Pro-inflammatory conditions may play an upstream role in suicide-related behavior, including neurotropic pathogens, traumatic brain injury and autoimmune disorders (Brundin et al., 2017). In a prospective analysis, those with higher levels of circulating C-reactive protein (CRP), a marker of systemic inflammation, had a greater risk of suicide after 9 years of follow up than those with lower levels of CRP (Batty et al., 2016).

Even less is known concerning whether relationships of inflammatory pathways with suicide-related behavior may be, at least in part, distinct from MD. Only a handful of studies indicate that such relationships exist (Black and Miller, 2015; Brundin et al., 2015; Cáceda et al., 2018; Falcone et al., 2010; O'Donovan et al. 2013). For example, among those with mood disorders, CRP levels are even higher among those with a recent suicide attempt (Loas et al., 2016). Furthermore, the role of external factors, capable of stimulating an inflammatory response, on suicide-related behavior and depressive symptoms is not well established.

Inflammatory signaling is part of the body's immune system and can be triggered by a wide range of challenges to host defense, including diet (Calder and Yaqoob, 2013) and environmental hazards such as particulate matter (Ma et al., 2017) and pollen (Galli et al., 2008). Different exposures may lead to different patterns of inflammatory activation, for example diet has been linked to inflammatory processes broadly (Minihane et al., 2015), while allergic responses are thought to primarily influence T helper (Th)2 cytokine signaling and reduced innate immune activation (Contoli et al., 2015). Elevated levels of white blood cells (WBC) and C-reactive protein (CRP) have been associated with mortality (Willems et

al., 2010) and chronic disease (B. J. Miller et al., 2015), including depression (Chamberlain et al., 2017; Wysoki ski and Margulska, 2017). Prior evidence demonstrates that diet can have both pro- and anti-inflammatory properties (Calder and Yaqoob, 2013; Galland, 2010) capable of stimulating pathways associated with neurobiology of mood disorders (Miller et al., 2009). Dietary inflammatory potential, measured using the Dietary Inflammatory Index® (DII), has previously been associated with cardiovascular disease (Garcia-Arellano et al., 2015), multiple types of cancer (Tabung et al., 2016) and depression (Bergmans and Malecki, 2017), but has not been studied in relation to suicide-related behavior. Seasonal pollen peaks have been associated with worsening symptoms of psychiatric disorders (Messias et al., 2010) and increased risk of completed suicide (Qin et al., 2013; Stickley et al., 2017) and suicide attempts (Jeon-Slaughter et al., 2016). However, exposure assessment is limited in prior studies (e.g. ecological design and averaging pollen counts over large geographic areas). Additionally, in a review of the literature (Kölves et al., 2015), associations between allergies and nonfatal suicide behaviors are mixed, indicating the need for further study.

The goal of this study was to use a large, nationally-representative sample of US adults to evaluate the relationship of multiple external inflammatory factors with suicide ideation, both within the context of MD and among those without current depression. Four inflammation-related measures were examined: immunoglobulin E (IgE), C-reactive protein (CRP), white blood cells (WBC), and dietary inflammatory potential. The primary hypothesis was that these four indicators of inflammation would be associated with suicidal ideation, independent of their association with depression.

2. Methods

2.1. Samples

Data come from the National Health and Nutrition Examination Survey (NHANES), a cross-sectional, population-based survey fielded annually, published biennially, and conducted by the National Center for Health Statistics (NCHS). NHANES assesses approximately 10,000 persons of all ages each 2-year cycle. The survey includes both a personal interview and an extensive clinical examination in which respondents provide venous blood samples. Prior to survey and exam data collection, informed consent was collected from study participants. NHANES was approved by the NCHS Research Ethics Review Board.

Due to changes in NHANES protocol over the past 15 years, not all variables of interest were collected in the same survey cycles. As a result, the analytic samples for this study come from three different cycles:

1. *Innate inflammation sample:* This analysis concatenated data from 3 cycles (2005/6 through 2009/10) to assess the relationship of CRP and WBC with suicidal ideation ($N_{\text{CRP\&WBC}} = 13,912$).
2. *Dietary inflammation sample:* This analysis concatenated data from 4 cycles (2007/8 through 2013/14) to assess the relationship dietary inflammatory potential with suicidal ideation ($N_{\text{DII}} = 17,076$).

3. *Allergy inflammation sample:* This analysis used data from the 2005/6 cycle to assess the relationship of IgE with suicidal ideation ($N_{\text{IgE}} = 4,060$).

All samples were limited to respondents aged 20 and older (younger respondents were not administered the depression measure). Missing data for complete-case analysis did not exceed 10%. NHANES is approved by the NCHS Research Ethics Review Board, protocol numbers 2005–06 and 2011–17 and all respondents provided informed consent.

2.2. Measures

2.2.1. Depression and suicidal ideation—Current MD was assessed using the Patient Health Questionnaire (PHQ-9), a brief depression assessment that assesses depressive symptoms over the past two weeks. The PHQ-9 is based on the Diagnostic and Statistical Manual for Mental Disorders (DSM) criteria for MD and has been extensively validated against clinical psychiatric interviews (Kroenke and Spitzer, 2002). This instrument assesses nine MD symptoms groups: little interest or pleasure in doing things; feeling down, depressed or hopeless; trouble falling asleep, staying asleep or sleeping too much; feeling tired or have little energy; poor appetite or overeating; feeling bad about themselves; trouble concentrating; speaking or moving so slowly that others could have noticed and; thoughts that they would be better off dead or of hurting themselves in some way. Each symptom is scored using a zero to three Likert scale reflecting the frequency of each symptom (i.e. not at all; several days; more than half the days, or; nearly every day). The PHQ-9 has a total possible score of 27, and validation studies recommend a score of 10 or more to identify those with current MD, which has a sensitivity and specificity of 88% relative to clinical psychiatric assessment of MD (Kroenke and Spitzer, 2002). Suicidal ideation was indicated by the symptom “*Thoughts that you would be better off dead or of hurting yourself in some way*” reported at a frequency of several days or more over the past two weeks.

In order to assess whether inflammation is associated with suicidal ideation independently from MD, a nominal four-level variable was created: suicidal ideation with MD (i.e., PHQ-9 score ≥ 10); suicidal ideation without MD; MD without suicidal ideation and; no MD and no suicidal ideation, which served as the reference group for all analyses.

2.2.2. WBC count and CRP—WBC, also known as leukocytes, are part of the body’s first line of defense against infection and contribute to a systemic response that can increase circulating cytokine levels and, subsequently, CRP (Arango Duque and Descoteaux, 2014). While the biological mechanisms and feedback loops that link WBC count and CRP are not fully understood (Vargas et al., 2016), both are used as clinical markers of inflammation.

WBC count was obtained using the Beckman Coulter method of counting and sizing in combination with an automatic diluting and mixing device for sample processing and a single- beam photometer for hemoglobinometry (Centers for Disease Control and Prevention, 2011a). CRP assays were performed on a Behring Nephelometer for quantitative CRP determination by latex-enhanced nephelometry (Centers for Disease Control and Prevention, 2011b). Both WBC and CRP levels were log transformed to normalize their distributions for analysis.

2.2.3. Dietary inflammatory potential—The Dietary Inflammatory Index® (DII) is a composite measure of the inflammatory potential of consumed foods. As described in detail elsewhere (Shivappa et al., 2014a; 2014b), the DII was developed following a review of almost 2,000 articles that evaluated the relationship of micronutrients and macronutrients with circulating levels of six inflammatory biomarkers: CRP, interleukin (IL) 1 β , IL-4, IL-6, IL-10 and tumor necrosis factor α (Shivappa et al., 2014a; 2014b). The DII has been validated against circulating levels of inflammatory markers, CRP and IL-6, in several population-based studies including NHANES (Shivappa et al., 2014a; 2014b; Tabung et al., 2015; Wirth et al., 2017; Shivappa et al., 2017).

DII scores were calculated using an average of dietary intake data from two 24 h dietary recalls. The first dietary recall was collected in person during the health examination and the second was collected via telephone three to 10 days later. Pro-inflammatory food parameters included in DII score were: total calories (kcal); carbohydrates (g); fat (g); protein (g); cholesterol (mg); total saturated fatty acids (g); iron (mg) and; vitamin B12 (μ g). Anti-inflammatory food parameters included in DII score were: alcohol (g); caffeine (g); fiber (g); total monounsaturated and polyunsaturated fatty acids (g); *n*-3 and *n*-6 polyunsaturated fatty acids (g); niacin (mg); riboflavin (mg); thiamin (mg); vitamins A (retinol equivalents), B6 (mg), C (mg), D (μ g), E (mg); β -carotene (μ g); magnesium (mg); selenium (μ g); zinc (mg) and; folate (μ g). Scores are centered at 0, with positive scores indicating an overall pro-inflammatory diet and negative scores indicating an overall anti-inflammatory diet. Continuous DII scores were then standardized (mean = 0, standard deviation = 1) to aid with interpretation.

Average total kilocalorie consumption, which is used as a control for the DII, was also calculated from these two 24 h dietary recalls. Adjustment for total energy consumption accounts for nutrient density (Willett, 2012).

IgE.: Several options exist for the measurement of allergic responses, including allergen skin test reactivity, circulating immunoglobulin E (IgE) levels, peripheral blood eosinophils, and the occurrence of allergic symptoms (Baldacci et al., 2001). These measures have been found to have only a weak relationship to each-other, as they represent different dimensions of underlying biological processes (Tollerud et al., 1991).

Serum samples from venous blood draw were analyzed for total IgE using the Pharmacia Diagnostics ImmunoCAP 1000 System (Gould and Sutton, 2008). Total IgE was log transformed for use in the analysis.

2.2.4. Covariates—Demographic characteristics included age, gender, race/ethnicity (Non-Hispanic White [reference group], Non-Hispanic Black, Hispanic, other), education attainment (< High School Degree [reference group], High School Degree or Equivalent, Some College, College Degree and Above), employment status (Working at a job or business [reference group]; Not working and not looking for work; Not working and looking for work) and marital status (Married or Living with Partner [reference]; Never Married; Separated, Divorced or Widowed).

Behavioral characteristics included smoking status, supplement use, physical activity, body mass index (BMI), antihistamine use and US region/seasonality of NHANES assessment. Smoking status was assessed by self-report and categorized as non-smoker [reference group], former smoker, current smoker. Binge drinking in the past 12 months was defined as

5 alcoholic beverages on average at a time for men and 4 alcoholic beverages for women. Physical activity was measured using two different self-report assessments, depending on the interview cycle: The Physical Activity Compendium (PAC) was used in 2005/6 and the Global Physical Activity Questionnaire (GPAQ) was used from 2007/9 to 2013/14. The PAC assesses physical activity for commuting to and from destinations, average level of physical activity each day, muscle strengthening activities, and tasks in or around the home and has been validated against doubly labeled water (Howell et al., 1999; Ainsworth et al., 2000). The GPAQ has moderate agreement with accelerometer data ($r = 0.48$) (Cleland et al., 2014). Both the PAC and the GPAQ estimating the amount of energy expended in metabolic equivalent (MET)-minutes per week. A MET-minute is the ratio of the amount of oxygen a person consumes while doing that activity for 1 minute per unit of body weight to the amount of oxygen a person consumes per unit of body weight during 1 minute of rest. This MET min/week score was calculated using previously developed formulas and cycle-specific survey weights (Johnson et al., 2013), then categorized into quartiles for analysis.

For the *Dietary inflammation sample* and the *Allergy inflammation sample*, binge drinking was included as a covariate. For the *Dietary inflammation sample*, this is because the DII, used to determine dietary inflammatory score, assigns alcohol a negative weight. Therefore, increasing levels of alcohol consumption are considered anti-inflammatory. However, evidence indicates that alcohol consumption has a U-shaped relationship with production of pro-inflammatory cytokines (Imhof et al., 2001). In other words, both abstaining from alcohol and excessive alcohol consumption is associated with greater dietary inflammatory potential when compared to moderate drinking, and thus binge drinking should be accounted for. Additionally, greater alcohol consumption is consistently associated with higher circulating levels of total IgE (Gonzalez-Quintela et al., 2004).

For the *Allergy inflammation sample*, both antihistamine use and U.S. region/seasonality of NHANES assessment were also accounted for. Use of antihistamines was assessed using the self-reported prescription data from NHANES. The NHANES prescription data was encoded using the Cerner Multum Lexicon Plus® drug database (Cerner Multum 2014). Medications reported with a first-level category of 122 (respiratory agents), and a second-level category of 123 (antihistamines) were classified as antihistamines. A single variable was created to account for both region of the country and season during data collection. The variable was created in this manner because the NHANES study collected data in the northern states during the summer months, and in the southern states during the winter months (National Center for Health Statistics (U.S.) 2013), creating complete confounding between region and season.

Finally, BMI was calculated from anthropometric measurements of weight and height. Since BMI has a curvilinear relationship with suicide ideation (Brown et al., 2018), BMI was

treated as categorical in analyses; i.e. underweight ($< 18.5 \text{ kg/m}^2$), normal weight ($18.5 \text{ to } < 25$), overweight ($25 \text{ to } < 30$) or obese (≥ 30) using World Health Organization guidelines.

2.3. Statistical analysis

In analyses of this study, inflammatory markers are treated as the outcomes of interest. The four-level categorical variable for MD and suicide ideation is treated as the exposure of interest. This allows for estimating mean levels of each inflammatory marker across the categories of MD and suicide ideation.

First, χ^2 and F tests were used to compare CRP, WBC count, DII score, IgE levels and covariates by the 4-level variable indicating MD and suicide ideation status. Next, a series of nested linear regressions were used to model the relationship between the four indicators of inflammation and suicide ideation/MD status. Model 1 accounted for demographic characteristics. Model 2 additionally accounted for health behaviors, which varied slightly by exposure of interest. For the *Innate Inflammation* analysis (i.e., CRP and WBC) Model 2 included smoking, BMI and physical activity. For the *Dietary Inflammation* analysis (i.e., DII score), Model 2 included smoking, BMI, physical activity, binge drinking, supplement use and average total kilocalories.

Finally, for the *Allergy Inflammation* analysis (i.e., IgE), Model 2 included smoking, BMI, binge drinking, physical activity, antihistamine use and U.S. region/seasonality. Due to a small number of individuals being classified as underweight (< 5) in the *Allergy Inflammation* sample, BMI was categorized as < 25 , $25 \text{ to } < 30$ and $\geq 30 \text{ kg/m}^2$.

Serum IgE levels reflect a combination of individual predisposition to allergies, previous allergic sensitizations, and recent allergen exposure, which may remain elevated after exposure to the allergen has ceased (Baldacci et al., 2001). This is important since in the absence of its target allergen, IgE will not provoke an immune or inflammatory response (Rosenwasser, 2011). Proliferation of eosinophils, a type of leukocyte involved in the immune response to allergens and parasites (Baldacci et al., 2001), may be more appropriate for detection of current allergic reactions (Kay et al., 1997; Tollerud et al., 1991). Therefore, a sensitivity analysis was conducted examining the use of eosinophil counts as an alternate measure of allergic response.

Another potential source of confounding may come from comorbid somatic conditions. NHANES collects information on diagnosis history of somatic conditions (including respiratory illness, cancer, cardiovascular disease, hyperlipidemia and high blood pressure). However, history of diagnosis may not reflect current comorbidities; therefore, adjustment for having a history of comorbid conditions is assessed in sensitivity analyses. Since susceptibility to infectious illnesses may be a potential pathway by which inflammatory measures evaluated in this study may increase risk of depression and suicide ideation, recent illness is not included in primary analyses. However, it is also possible that recent illness leads to changes in dietary consumption as well as circulating levels of inflammatory markers. Therefore, sensitivity analyses in the *Innate Inflammation* and *Dietary Inflammation* sample assess confounding by recent illness due to head cold, chest cold, flu, pneumonia, ear infection, stomach illness or intestinal illness.

All analyses were conducted using SAS® (version 9.4, Cary, NC) using SAS survey procedures. In variance computation, missing values were treated as not missing completely at random (NOMCAR). This allows for analyzing complete case data as a subpopulation, where the total population contains subjects with both non-missing and missing observations (Buskirk, 2011). Sampling weights appropriate for the two-cycles (*Allergy*), six-cycles (*Dietary*) and eight-cycles (*Innate*), respectively, were calculated and used in all analyses. Sampling weights correct for unequal probability of selection across participants. Further, the sample weights for the Dietary analysis also accounts for non-response specific to dietary recalls and the proportion of weekend-weekday combinations of dietary recalls across individuals. This is necessary because proportionally more NHANES exams occurred on weekend days than on weekdays.

3. Results

Table 1 presents descriptive statistics by suicidal ideation and MD status. For all three analytic subsamples, respondents with MD – regardless of whether they reported suicidal ideation or not, were more likely to be younger, female, and unemployed.

Table 2 presents the relationship between MD and suicidal ideation with CRP and WBC count in the *Innate Inflammation* analytic sample. In the crude models, MD was associated with higher CRP regardless of suicidal ideation ($\beta_{MDIdeation} = 0.28$, $\beta_{MDNoIdeation} = 0.44$); ideation without MD was not associated with CRP even in the crude model ($\beta_{IdeationNoMD} = 0.09$). In fully adjusted models, only those who did not endorse suicide ideation and met MD criteria had higher CRP ($\beta_{MDNoIdeation} = 0.13$; 95% CI = 0.03 to 0.22) relative to the group with neither MD nor ideation. CRP was not elevated among those with suicidal ideation with or without MD. When adjusting for comorbid somatic conditions, results remained unchanged (data not shown). When adjusting for recent illness, MD and suicide ideation were not associated with CRP levels (data not shown).

A similar pattern was seen for WBC, although these differences were smaller in magnitude and did not reach traditional levels of statistical significance (p -value = 0.0716). When including history of comorbid somatic conditions in the model, those without suicide ideation and met MD criteria had higher WBC levels compared to the reference ($\beta_{MDNoIdeation} = 0.03$; 95% CI = 0.00 to 0.06; p -value = 0.0462) (data not shown). When adjusting for recent illness, again there was no association of MD and suicide ideation with WBC (data not shown).

Table 3 presents the relationship between MD and suicidal ideation with standardized DII scores in the *Dietary Inflammation* analytic sample. As with the first analysis, MD was related to DII score remains, regardless of suicidal ideation. Suicidal ideation without MD was associated with modestly a modestly higher DII score ($\beta_{IdeationNoMD} = 0.15$, 95% CI: 0.03 – 0.27) relative to neither MD nor ideation. However, MD – regardless of ideation – was also related to significantly higher DII scores ($\beta_{MDIdeation} = 0.22$, $\beta_{MDNoIdeation} = 0.21$). When accounting for comorbid conditions and recent illness, results remain unchanged (data not shown).

Table 4 presents the relationship between MD and suicidal ideation with IgE in the *Allergy* analytic sample. There was no statistically significant relationship between MD or ideation with IgE, whether in the crude or adjusted models. Additionally, serum eosinophil concentrations were not associated with MD or ideation (data not shown). Adjusting for comorbid conditions did not change these findings.

4. Discussion

This study assessed whether three types of inflammatory indicators – innate immune markers, dietary inflammatory potential, and markers of allergic response – distinguish between MD and suicidal ideation in a general population sample of adults. The primary finding is while several inflammatory indicators are associated with depressive symptoms, they do not differ between depression cases with and without suicidal ideation. That is, contrary to our hypothesis, suicidal ideation was not associated with a unique pro-inflammatory state among individuals with depression.

In the analysis of innate immunity, CRP, and to some extent WBC, were highest among those who met criteria for MD but did not endorse ideation. A recent meta-analysis of both clinical and community populations reported that CRP is higher among MD cases compared to controls, however this study did not distinguish between MD with versus without suicidal ideation (Howren 2009). In a study of 124 patients with MD, O'Donovan et al. (2013) found that CRP was not associated with suicidal ideation (O'Donovan et al., 2013), consistent with findings of this study. More recently, a meta-analysis (Black and Miller, 2015) and a study of 52 patients with MD (Cáceda et al., 2018) also concluded that while CRP may identify those with MD from non-psychiatric controls, it does not appear to distinguish suicide ideation among patients with MD (Black and Miller, 2015; Cáceda et al., 2018). Worth noting, prior work has observed suicidal ideation to be associated with other markers of inflammation, including serum S100B (Falcone et al., 2010) and IL-1 β and IL-6 (Black and Miller, 2015), even after accounting for depression status. IL-6 is one of the inflammatory cytokines that influences activity of the kynurenine pathway.

MD, regardless of suicidal ideation, was associated with higher pro-inflammatory DII scores. In contrast to the analysis of innate immunity, suicidal ideation was also associated with a more pro-inflammatory DII score in individuals without MD, although this relationship was more modest than the relationship between MD and DII. This is the first study, to the authors' knowledge, to test whether the relationship between dietary inflammatory potential and suicidal behavior is distinct from MD. Previous analyses have demonstrated that dietary inflammatory potential is prospectively associated with depression and depressive symptoms (Sánchez-Villegas et al., 2015; Tabung et al., 2016). Additionally, the association of DII with MD and mental distress has been observed within NHANES (Bergmans and Malecki, 2017). However; this prior work has not examined the relationship between suicide ideation and dietary inflammatory potential. In possibly related work, higher BMI, indicative of obesity, has a paradoxical association with suicide—higher BMI is associated with greater depression yet lower rates of completed suicide, especially in men (Klinitzke et al., 2013; Zhang et al., 2013). Even in studies that account for depression, this

trend remains (Zhang et al., 2013). Future research may consider whether differences in diet quality and dietary inflammation across BMI categories contributes to this relationship.

Findings from this study should be interpreted in light of study limitations. NHANES is a cross-sectional survey and the MD and inflammatory indicators were measured contemporaneously, which precludes any interpretation regarding temporality. Additionally, NHANES does not allow for adjustment of comorbid psychiatric illnesses, which may confound associations of inflammatory factors with depression and suicide ideation. Given social stigma concerning mental health, symptoms of MD and suicidal ideation may be underreported (Bharadwaj et al., 2017); assuming that this measurement error is non-differential relative to the inflammatory indicators, this would bias our results toward the null (Kristensen, 1992). While the 24 h dietary recall is not a direct measure of dietary intake, taking an average of two measures reduces intrasubject variation; NHANES also uses an automated five-step multiple-pass approach which aids in the collection of complete 24 h diet recalls (Steinfeldt et al., 2013). Further, limited standardization of blood collection protocol is a weakness. NHANES blood collection appointments were scheduled throughout the day (i.e. morning and afternoon). Only those who were scheduled for a morning appointment were instructed to fast 9 h prior however; this was not a requirement for a sample to be included in the final sample (Centers for Disease Control and Prevention, n.d.). Unless those with elevated CRP, WBC, etc. were systematically more likely have their blood drawn in the afternoon vs. morning (which seems unlikely), any noise introduced by this lack of fasting would bias results toward the null.

Of final consideration, suicide ideation was an outcome of interest in this study, and risk factors for suicide ideation differ from risk factors of other suicidal behaviors, such as attempts (Nock et al., 2016). However, even the single item from the PHQ-9 assessing suicide ideation predicts suicide attempts and death due to suicide (Simon et al., 2013), indicating that the measure used in study analyses estimates vulnerability beyond short-term crisis. Regardless, future research may consider whether inflammatory states distinguish suicidal behaviors and the role of inflammatory pathways in transitions from suicide ideation to suicide attempt.

This study also has several strengths, including the large, population-based sample of U.S. adults and use of sampling weights that account for non-response. Prior research within clinical settings is susceptible to confounding due to access to care and severity of cases. While generalizability of results may be limited within a clinical setting, findings are relevant at a population level. This paper also examined three diverse types of inflammatory indicators – innate immunity, dietary inflammatory potential, and markers of allergic response – and thus provides among the most comprehensive assessment of the relationship between depression, suicidal ideation and inflammation conducted to date.

In summary, pro-inflammatory mechanisms associated with innate immunity, dietary exposures, and allergic responses do not distinguish MD with suicidal ideation from MD without suicidal ideation. Dietary inflammatory potential is associated with suicidal ideation among individuals without MD. Additional research is needed to determine whether

improving diet quality and reducing consumption of pro-inflammatory foods may reduce suicidal ideation.

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Abbreviations:

MD	major depression
SI	suicidal ideation
NHANES	National Health and Nutrition Examination Survey
CRP	C-reactive protein
WBC	white blood cell
IgE	immunoglobulin E
DII	Dietary Inflammatory Index®
IL	interleukin
NCHS	National Center for Health Statistics
PHQ-9	Patient Health Questionnaire 9-Item
PAC	Physical Activity Compendium
GPAQ	Global Physical Activity Questionnaire
BMI	body mass index
Th	T helper
CI	confidence interval

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Descriptive statistics by suicidal ideation endorsement and depression status across three samples of the National Health and Nutrition Examination Survey (NHANES)^a.

	Do not endorse suicidal ideation		Endorse suicidal ideation		P value
	Not depressed	Depressed	Not depressed	Depressed	
Innate inflammation sample					
Age group (n, %)					<0.0001
20 to < 40	4,297 (36.9)	303 (35.7)	60 (32.4)	101 (34.3)	
40 to < 65	5,126 (45.7)	446 (54.4)	91 (50.2)	187 (55.3)	
65 and Older	3,093 (17.4)	118 (9.9)	48 (17.4)	42 (10.4)	
Race (n, %)					<0.0001
Non-hispanic white	6,306 (72.2)	408 (66.5)	86 (62.0)	120 (56.2)	
Non-hispanic black	2,372 (10.1)	182 (14.7)	23 (7.2)	77 (18.0)	
Hispanic	3,337 (12.3)	246 (13.8)	85 (25.4)	121 (22.1)	
Other	501 (5.4)	31 (4.9)	5 (5.4)	12 (3.7)	
Male (n, %)	6298.0 (49.7)	289.0 (33.0)	97.0 (48.3)	134.0 (44.2)	<0.0001
Educational attainment (n, %)					<0.0001
< High School Degree	3,342 (17.1)	333 (29.0)	82 (32.1)	151 (33.2)	
High School Degree or Equivalent	2,980 (23.9)	220 (29.1)	51 (24.9)	70 (23.5)	
Some College	3,496 (30.5)	236 (30.5)	44 (28.0)	87 (33.7)	
College Degree and Above	2,698 (28.5)	78 (11.5)	22 (14.9)	22 (9.6)	
Employment status (n, %)					<0.0001
Employed	7,354 (67.7)	316 (41.4)	86 (50.3)	116 (43.9)	
Unemployed and not looking for work	4,853 (30.0)	516 (55.1)	105 (46.6)	205 (52.7)	
Unemployed and looking for work	309 (2.3)	35 (3.4)	8 (3.1)	9 (3.4)	
Marital status (n, %)					<0.0001
Married or living with partner	7,901 (66.6)	435 (53.5)	99 (54.5)	154 (46.8)	
Single	1,961 (16.0)	155 (16.6)	45 (23.2)	71 (20.6)	
Separated, divorced or widowed	2,654 (17.4)	277 (29.9)	55 (22.3)	105 (32.5)	
Smoking status (n, %)					<0.0001
Non-smoker	6,715 (53.8)	353 (37.7)	107 (52.8)	122 (38.9)	

	Do not endorse suicidal ideation		Endorse suicidal ideation		P value
	Not depressed	Depressed	Not depressed	Depressed	
Former smoker	3,251 (25.5)	182 (20.7)	43 (19.0)	58 (16.7)	<0.0001
Current smoker	2,550 (20.8)	332 (41.6)	49 (28.2)	150 (44.3)	
Weight status (n, %)					
Underweight	181 (1.6)	13 (1.4)	6 (2.4)	6 (1.7)	<0.0001
Normal weight	3,428 (30.1)	198 (24.7)	48 (25.8)	89 (29.0)	
Overweight	4,387 (34.1)	243 (29.1)	75 (36.9)	95 (26.8)	<0.0001
Obese	4,520 (34.2)	413 (44.9)	70 (34.8)	140 (42.5)	
Physical activity (n, %)					
MET ^e minutes/week Q1	3,512 (22.9)	372 (40.9)	79 (33.3)	132 (36.8)	<0.0001
MET ^e minutes/week Q2	3,042 (25.2)	190 (22.0)	31 (18.0)	65 (18.3)	
MET ^e minutes/week Q3	2,967 (26.3)	151 (18.9)	44 (26.8)	62 (18.3)	<0.0001
MET ^e minutes/week Q4	2,995 (25.5)	154 (18.2)	45 (21.9)	71 (26.5)	
Health status (n, %)					
Excellent or very good	5,495 (52.1)	123 (15.4)	51 (32.8)	39 (15.3)	<0.0001
Good	4,506 (34.1)	273 (35.3)	72 (34.7)	89 (30.2)	
Fair or poor	2,509 (13.7)	471 (49.3)	76 (32.5)	202 (54.5)	<0.0001
C-reactive protein^f (mean, 95% CI)	-1.6 (-1.7, -1.6)	-1.3 (-1.4, -1.2)	-1.6 (-1.8, -1.5)	-1.4 (-1.6, -1.3)	
White blood cell count^f (mean, 95% CI)	1.94 (1.93, 1.94)	2.01 (1.99, 2.03)	1.94 (1.91, 1.98)	1.97 (1.94, 2.00)	<0.0001
Dietary inflammation sample					
Age group (n, %)					
20 to < 40	5,021 (36.5)	375 (36.6)	61 (38.3)	121 (33.3)	<0.0001
40 to < 65	6,487 (45.5)	615 (52.0)	88 (44.7)	240 (56.0)	
65 and Older	3,772 (18.0)	179 (11.5)	50 (17.0)	67 (10.6)	<0.0001
Race (n, %)					
Non-hispanic white	7,159 (69.4)	538 (64.4)	90 (62.6)	171 (55.5)	<0.0001
Non-hispanic black	3,170 (10.8)	251 (13.4)	31 (10.4)	89 (15.6)	
Hispanic	3,606 (13.3)	300 (15.3)	66 (20.1)	147 (24.1)	<0.0001
Other	1,345 (6.5)	80 (6.9)	12 (7.0)	21 (4.8)	

	Do not endorse suicidal ideation		Endorse suicidal ideation		P value
	Not depressed	Depressed	Not depressed	Depressed	
Male (n, %)	7592.0 (49.2)	383.0 (33.5)	93.0 (45.0)	168.0 (42.9)	<0.0001
Educational attainment (n, %)					<0.0001
< High School Degree	3,407 (15.0)	417 (26.8)	68 (26.7)	175 (31.7)	
High School Degree or Equivalent	3,490 (21.8)	278 (27.2)	46 (26.1)	95 (26.7)	
Some College	4,532 (31.3)	352 (35.6)	48 (26.5)	115 (28.8)	
College Degree and Above	3,851 (31.9)	122 (10.5)	37 (20.7)	43 (12.8)	
Employment status (n, %)					<0.0001
Employed	8,721 (64.0)	399 (38.8)	87 (51.6)	137 (39.5)	
Unemployed and not looking for work	6,070 (33.0)	730 (57.1)	105 (45.3)	276 (57.5)	
Unemployed and looking for work	489 (3.0)	40 (4.0)	7 (3.1)	15 (3.0)	
Marital status (n, %)					<0.0001
Married or living with partner	9,418 (64.6)	545 (46.3)	93 (51.0)	190 (46.6)	
Single	2,706 (18.6)	232 (21.0)	47 (25.6)	90 (26.1)	
Separated, divorced or widowed	3,156 (16.7)	392 (32.7)	59 (23.4)	148 (27.3)	
Smoking status (n, %)					<0.0001
Non-smoker	8,631 (57.1)	487 (38.8)	111 (55.4)	172 (41.8)	
Former smoker	3,857 (25.1)	256 (19.1)	50 (24.0)	89 (20.3)	
Current smoker	2,792 (17.8)	426 (42.1)	38 (20.5)	167 (37.9)	
Weight status (n, %)					<0.0001
Underweight	223 (1.4)	18 (1.4)	5 (1.7)	7 (1.2)	
Normal weight	4,178 (29.2)	247 (23.9)	47 (19.9)	97 (25.8)	
Overweight	5,229 (34.0)	304 (28.3)	73 (41.1)	120 (25.5)	
Obese	5,650 (35.4)	600 (46.4)	74 (37.4)	204 (47.5)	
Alcohol use (n, %)					<0.0001
Abstain	4,876 (26.1)	439 (31.3)	75 (32.3)	174 (37.1)	
mild to moderate ^b	8,652 (61.8)	552 (52.4)	98 (45.7)	178 (46.9)	
heavy ^c	1,752 (12.1)	178 (16.3)	26 (22.0)	76 (16.1)	
Physical activity (n, %)					<0.0001
ME/Te minutes/week Q1	4,139 (22.6)	505 (41.6)	73 (28.9)	176 (37.3)	
ME/Te minutes/week Q2	3,690 (24.5)	258 (22.2)	38 (28.3)	91 (20.2)	

	Do not endorse suicidal ideation		Endorse suicidal ideation		P value
	Not depressed	Depressed	Not depressed	Depressed	
ME/Te minutes/week Q3	3,683 (26.7)	180 (16.6)	46 (23.0)	72 (19.0)	
ME/Te minutes/week Q4	3,768 (26.2)	226 (19.6)	42 (19.8)	89 (23.5)	
Use supplements (n, %)	7,517 (45.8)	623 (53.6)	101 (47.9)	256 (58.3)	<0.0001
Total energy consumption (mean, 95% CI)	2,039 (2,026, 2,052)	1,930 (1,885, 1,975)	2,006 (1,895, 2,118)	1,953 (1,864, 2,043)	<0.0001
Dietary inflammatory index score (mean, 95% CI)	0.0 (-0.1, 0.0)	0.4 (0.3, 0.4)	0.1 (0.0, 0.2)	0.4 (0.3, 0.5)	<0.0001
Allergy inflammation Sample					
Age group (n, %)					0.0788
20 to < 40	1438 (37.5)	57 (32.7)	21 (36.9)	26 (32.1)	
40 to < 65	1441 (45.5)	95 (57.4)	22 (45.8)	39 (57.7)	
65 and Older	872 (17.1)	26 (9.9)	14 (19.2)	9 (10.2)	
Race (n, %)					<0.0001
Non-hispanic white	1967 (74.6)	84 (69.2)	20 (48.3)	27 (59.5)	
Non-hispanic black	84 (69.2)	51 (15.8)	9 (9.3)	26 (20.0)	
Hispanic	860 (10.6)	38 (10.4)	27 (37.6)	17 (14.0)	
Other	134 (4.6)	5 (4.6)	1 (4.8)	4 (6.4)	
Male (n, %)	1830 (48.9)	67 (36.0)	25 (43.2)	32 (46.4)	0.0154
Educational attainment (n, %)					<0.0001
< High School Degree	965 (16.0)	63 (26.6)	24 (36.3)	25 (17.7)	
High School Degree or Equivalent	882 (24.3)	50 (32.0)	18 (32.6)	21 (35.6)	
Some College	1086 (31.7)	50 (32.2)	12 (20.0)	24 (37.6)	
College Degree and Above	818 (28.0)	15 (9.2)	3 (11.1)	4 (9.1)	
Employment status (n, %)					<0.0001
Employed	2310 (70.0)	66 (42.5)	19 (42.9)	23 (20.2)	
Unemployed and not looking for work	1378 (28.4)	106 (54.4)	34 (50.9)	50 (58.4)	
Unemployed and looking for work	63 (1.6)	6 (3.1)	4 (6.2)	1 (1.3)	
Marital status (n, %)					<0.0001
Married or living with partner	2435 (67.7)	102 (61.8)	29 (51.4)	36 (43.1)	
Never married	555 (14.3)	22 (12.2)	13 (23.5)	15 (17.4)	
Separated, divorced or widowed	761 (18.0)	54 (26.0)	15 (25.0)	23 (39.5)	
Smoking status (n, %)					<0.0001

	Do not endorse suicidal ideation		Endorse suicidal ideation		P value
	Not depressed	Depressed	Not depressed	Depressed	
Non-smoker	1979 (51.3)	67 (32.9)	30 (55.9)	29 (42.5)	
Former smoker	990 (25.6)	42 (23.5)	8 (8.3)	15 (21.2)	
Current smoker	782 (23.1)	69 (43.6)	19 (35.8)	30 (36.3)	
Weight status (n, %)					0.0475
Under or normal weight	1120 (32.5)	46 (27.6)	18 (34.6)	26 (36.3)	
Overweight	1316 (33.1)	50 (25.9)	24 (40.7)	19 (22.4)	
Obese	1315 (34.4)	82 (46.6)	15 (24.7)	29 (41.3)	
Drinking (n, %)					0.1030
Abstain	1291 (27.7)	64 (32.5)	23 (38.8)	27 (25.8)	
Mild to moderate ^b	2008 (59.4)	79 (47.4)	29 (50.2)	39 (61.6)	
Heavy ^c	452 (13.0)	35 (20.1)	5 (11.0)	8 (12.7)	
Physical activity (n, %)					<0.0001
MET ^e minutes/week Q1	1220 (27.4)	89 (45.9)	24 (35.4)	39 (49.6)	
MET ^e minutes/week Q2	791 (22.6)	26 (15.4)	7 (16.8)	9 (10.5)	
MET ^e minutes/week Q3	869 (25.0)	34 (22.3)	13 (23.3)	10 (10.9)	
MET ^e minutes/week Q4					
Antihistamine use (n, %)	131 (4.6)	10 (5.5)	1 (1.9)	4 (6.9)	0.6096
Region/season (n, %)					0.2311
North/summer	2064 (59.5)	86 (51.6)	38 (69.3)	34 (53.3)	
South/winter	1687 (40.5)	92 (48.4)	19 (30.7)	40 (46.7)	
Total IgE (kU/L, 95% CI)	130.2 (113.9–146.4)	132.8 (92.7–172.9)	113.4 (69.6–157.2)	118.5 (55.7–181.4)	0.6893

^a Cell values represent column percents unless otherwise indicated.

^b For men, 1–4 drinks at a time; for women, 1–3 drinks at a time.

^c For men, 5 drinks at a time; for women, 4 drinks at a time.

^d Physical activity quartiles are NHANES cycle specific.

^e MET = Metabolic Equivalent of Task.

^f natural log transformed.

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Total kilocalories consumed based on an average of two 24 h dietary recalls.
 S_y Standardized (mean = 0, standard deviation = 1).

Table 2

Circulating inflammatory markers by depression and suicidal ideation status among adults, NHANES^a 2005–2010.

	Do not endorse suicidal ideation		Endorse suicidal ideation	
	Not depressed	depressed	Not depressed	Depressed
	<i>n</i> =12,516	<i>n</i> =867	<i>n</i> =199	<i>n</i> =330
log C-reactive protein				
	<i>R</i> ²	b (95% CI)	b (95% CI)	<i>P</i> value
Crude	0.00	Ref.	0.44 (0.35, 0.54)	0.28 (0.14, 0.42)
Model 1	0.00	Ref.	0.31 (0.21, 0.41)	0.15 (0.02, 0.29)
Model 2	0.00	Ref.	0.13 (0.03, 0.22)	0.04 (−0.09, 0.17)
log white blood cell count				
	<i>R</i> ²	b (95% CI)	b (95% CI)	<i>P</i> value
Crude	0.00	Ref.	0.09 (0.07, 0.12)	0.04 (0.00, 0.09)
Model 1	0.00	Ref.	0.07 (0.04, 0.09)	0.03 (−0.01, 0.07)
Model 2	0.00	Ref.	0.03 (0.01, 0.06)	0.00 (−0.04, 0.03)

Model 1 accounts for age group, race, gender, educational attainment, employment status and marital status.

Model 2 accounts for all variables in Model 1, plus smoking status, weight status, physical activity and perceived health status.

^aNational Health and Nutrition Examination Survey.

Table 3

Association of dietary inflammatory index (DII) score by MD and suicidal ideation status among adults, NHANES^a 2007–2014.

	No suicidal ideation		Suicidal ideation		<i>P</i> value
	No MD <i>n</i> =15,280	MD <i>n</i> =1,169	No MD <i>n</i> =199	MD <i>n</i> =428	
Standardized DII score					
<i>R</i> ²	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	
Crude	0.02 Ref.	0.53 (0.45, 0.61)	0.23 (0.03, 0.42)	0.53 (0.36, 0.69)	< 0.001
Model 1	0.14 Ref.	0.30 (0.22, 0.38)	0.10 (−0.06, 0.27)	0.33 (0.17, 0.49)	< 0.001
Model 2	0.45 Ref.	0.21 (0.15, 0.27)	0.15 (0.03, 0.27)	0.22 (0.11, 0.33)	< 0.001

Model 1 accounts for age group, race, gender, educational attainment, employment status and marital status.

Model 2 accounts for all variables in Model 1, plus smoking status, weight status, alcohol use, physical activity, supplement use and total energy consumption.

^aNational Health and Nutrition Examination Survey.

Association of circulating IgE plasma levels by MD and Suicidal Ideation Status among Adults, NHANES^a 2007–2014.**Table 4**

ln IgE (log(kU/L))	No suicidal ideation			Suicidal ideation		
	No MD		MD	No MD		MD
	n=3,751		n=179	n=58		n=74
	R ²	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	P value
Crude	0.00	Ref.	0.07 (−0.21,0.33)	0.10 (−0.38,0.58)	0.02 (−0.36,0.39)	0.9300
Model 1	0.08	Ref.	0.03 (−0.24,0.30)	−0.09 (−0.55,0.36)	−0.16 (−0.47,0.15)	0.7096
Model 2	0.09	Ref.	0.01 (−0.27,0.26)	−0.07 (−0.55,0.40)	−0.17 (−0.46,0.11)	0.6308

Model 1 accounts for age group, race, gender, educational attainment, employment status and marital status.

Model 2 accounts for all variables in Model 1, plus smoking status, weight status, alcohol use, physical activity, antihistamine use and U.S region/seasonality of NHANES data collection.

^aNational Health and Nutrition Examination Survey.