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Family-Based Analyses Reveal Novel Genetic Overlap Between Cytokine Interleukin-8 and Risk for Suicide Attempt

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Abstract

Background—Suicide is major public health concern. It is imperative to find robust biomarkers so that at-risk individuals can be identified in a timely and reliable manner. Previous work suggests mechanistic links between increased cytokines and risk for suicide, but questions remain regarding the etiology of this association, as well as the roles of sex and BMI.

Methods—Analyses were conducted using a randomly-ascertained extended-pedigree sample of 1882 Mexican-American individuals (60% female, mean age=42.04, range=18-97). Genetic correlations were calculated using a variance components approach between the cytokines TNF-α, IL-6 and IL-8, and Lifetime Suicide Attempt and Current Suicidal Ideation. The potentially confounding effects of sex and BMI were considered.

Results—159 individuals endorse a Lifetime Suicide Attempt. IL-8 and IL-6 shared significant genetic overlap with risk for suicide attempt (ρ_g=0.49, p_{FDR}=7.67x10^{-3}; ρ_g=0.53, p_{FDR}=0.01), but for IL-6 this was attenuated when BMI was included as a covariate (ρ_g=0.37, se=0.23, p_{FDR}=0.12). Suicide attempts were significantly more common in females (p_{FDR}=0.01) and the

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genetic overlap between IL-8 and risk for suicide attempt was significant in females (ρ_g=0.56, p_{FDR}=0.01), but not in males (ρ_g=0.44, p_{FDR}=0.30).

Discussion—These results demonstrate that: IL-8 shares genetic influences with risk for suicide attempt; females drove this effect; and BMI should be considered when assessing the association between IL-6 and suicide. This finding represents a significant advancement in knowledge by demonstrating that cytokine alterations are not simply a secondary manifestation of suicidal behavior, but rather, the pathophysiology of suicide attempts is, at least partly, underpinned by the same biological mechanisms responsible for regulating inflammatory response.

Keywords

suicide; inflammation; genetics; biomarkers; mood

Introduction

A recent report by the Centers for Disease Control and Prevention indicated that in the United States alone suicide rates increased by more than 30% between 1999 and 2016[1] making suicide a leading cause of death. Moreover, this report does not account for the fact that suicide *attempts* are grossly underreported, with twenty or more attempts estimated for every completion [2,3].

The need for biomarkers to identify suicide risk in an effective and timely manner has never been greater. Biomarkers are objective indicators of illness risk [4] and one potential biomarker of suicide is inflammation. There is strong evidence for altered levels of inflammation in individuals experiencing suicidality, particularly in pro-inflammatory cytokines TNF-α, IL-6 and IL-8 [5,6]. This association has been demonstrated in several psychiatric disorders, in both the periphery and central nervous system, in individuals that have either attempted or completed suicide, and in a plethora of centrally- and peripherally-measured cytokines [7-23].

However, important questions remain regarding the relationship between TNF-α, IL-6 and IL-8 and risk for *lifetime suicide attempt* or *current suicidal ideation.* First, the etiologic origins of the relationship are unclear. Risk for suicide has been shown to be heritable [24] as have levels of TNF-α, IL-6 [25,26] and IL-8 [27]. However, no study has attempted to assess any potential overlap in the genetic factors that influence inflammation and suicide risk. Therefore, it is not known whether inflammation is directly involved in the pathophysiology of suicidal behavior, or arises as a secondary manifestation of these behaviors.

Second, despite consistent sex differences in both suicidal behavior and immune response, the effect of sex is rarely examined [28]. Males more often complete suicide than females (although recent trends indicate that that gap is narrowing [29]). Paradoxically, females make, on average, twice as many suicide attempts as males. This difference in mortality rates is thought to stem from males more often choosing violent and lethal suicide methods than females [30]. There are also sex differences in how the immune system responds to both foreign and self-antigens [31]. In general, female immune responses tend to be stronger, resulting in greater immunity (e.g. enhanced vaccine response), but also increased

susceptibility to inflammatory and autoimmune diseases [28,32,34]. A handful of studies on suicidal behavior have assessed the impact of sex on inflammation levels [9,35-40], but no study, to date, has tested whether any genetic overlap between inflammation and risk for suicidal behavior varies as a function of sex. Evidence for genetic overlap in one sex but not the other might hint at important differences between males and females in the pathophysiology of suicidal behavior.

Third, increased adiposity is a well-established correlate of inflammation [41], but studies on the relationship between inflammation and suicide have generally not examined the effect of adiposity on this relationship, or treated it as a nuisance covariate [9,11,39]. In particular, IL-6 production is thought to increase with adiposity, which is typically measured using its proxy body mass index (BMI), with up to a third of circulating IL-6 originating from adipose tissue [42-44]. Evidence for a link between suicide and BMI is mixed [45]. Some studies report an inverse association between BMI and suicide completion [46-48] and attempt [49-51], while others report a positive association with completions [52,53] and attempts [54-56]. Of the four studies on suicidal behavior that tested the influence of BMI on inflammation, three indicated that BMI had no significant effect [13,37,38], and one showed that BMI was significantly associated with inflammation [57]. Thus, current evidence for an association between BMI, inflammation and suicide, is mixed.

Previous studies have been unable to provide answers to these questions. Family-based data (e.g. twins or extended pedigrees) are the gold standard for establishing the extent of genetic influence (i.e. heritability) on individual traits, as well as genetic overlaps (i.e. genetic correlation) between traits, but no study on inflammation and suicide has been conducted in families. Moreover, a sizable sample is required for such studies and while one of the more recent studies looking at the relationship between IL-6 and suicide had a relatively large sample (N = 784, [9]), many studies prior to that had samples of less than or just over one-hundred individuals [6]. These sample sizes and lack of statistical power may partly account for why the effects of sex and BMI have been difficult to pin down.

Using a large, multi-generational, multi-family sample of 1882 Mexican-American individuals combined with univariate and multivariate variance components methods we present the first study to disentangle shared genetic effects on suicidal behavior and cytokine levels. We chose to investigate the shared genetic influences of cytokines and suicide because of robust associations between risk for suicidal behavior and cytokine levels. In the blood-based assay available in the sample three cytokines were present at detectable levels for subsequent analysis to take place: IL-6, IL-8 and TNF-α. The aims of this study were threefold, to establish: (a) the degree of genetic overlap between both *lifetime suicide attempt* and *current suicidal ideation* and three different cytokines; (b) the extent to which the genetic overlap between IL-6, over and above IL-8, is confounded by BMI; and (c) whether the genetic overlap between risk for suicide and either interleukin was sex-specific.

Methods

Participants

The sample comprised 1882 individuals from extended pedigrees (83 families, mean size = 21.67 individuals, range 2-178 individuals). The sample was 60.43% female and had a mean age of 42.04 years (sd = 15.74 years, range = 18-97 years). Individuals in this Genetics of Brain Structure and Function Study (GOBS) have actively participated in research for over 18 years and were randomly selected from the community. Inclusion criteria were: 1) Mexican American ancestry, 2) part of a large family, and 3) live within the San Antonio region (see [58] for recruitment details). All participants provided written informed consent on forms approved by the institutional review board at the University of Texas Health Science Center of San Antonio.

Suicide Assessment

Participants completed the semi-structured Mini-International Neuropsychiatric Interview (MINI;[59]). Interviews were conducted by masters- and doctorate-level research staff who had established reliability for conducting suicide risk assessment (κ 0.85). Suicidality was assessed in two ways in the present study, both assessments were taken from Section C of the MINI. *Lifetime Suicide Attempt* was assessed by item C6: 'Did you ever make a suicide attempt?'. Our Lifetime Suicide Attempt index is therefore a dichotomous trait, with a score of 1 indicating a "yes" response and 0 indicating a "no" response. The MINI also includes a section on current suicidality (items C1-C5), asking whether in the past month the participant thought they would be better off dead (C1); wished that they were dead (C2); wanted to harm themselves (C3); thought about suicide (C4); or had a suicide plan (C5). These items were collapsed to generate a categorical index of *Current Suicidal Ideation,* with a score of 1 indicating that any item between C1-C5 was endorsed and a score of 0 indicating that none were endorsed. The presence of major depressive, anxiety, alcohol and substance use disorders was also evaluated as part of the MINI assessment. Subjects who reported possible pathology were discussed in case conference meetings with licensed psychologists and/or psychiatrists. Consensus diagnoses for major depressive disorder and a lifetime suicide attempt were determined using available medical records, the MINI, and the interviewer's narrative.

Inflammation Measurement

Participants completed a venipuncture between the hours of 7am and 11am for the measurement of inflammation markers. Blood was drawn after a 12-hr fast. Blood samples were centrifuged for 20 min at 4°C, aliquoted in 50uL volumes (chiclets) of EDTA plasma and stored at −80°C within 4 h ofvenipuncture. Inflammation assays were run in plasma using a Milliplex MAP Human Adipokine Magnetic Bead Panel 2 (Millipore catalog #HADK2MAG-61K) on a Luminex 200 instrument. The cytokines run were TNF-α, IL-6 and IL8. Assays were performed in 96-well plates on plasma samples stored at −80°C. 10% of the samples were run in duplicate on separate plates. Intra-assay coefficients of variation were <10% for all markers. Minimum detectable concentration (pg/mL) was 0.2, 0.3, and 0.3 for IL-6, IL-8 and TNF-α respectively.

Quantitative Genetic Analysis

All genetic analyses were performed in SOLAR [60]. SOLAR implements a maximum-likelihood variance decomposition approach to determine the proportions of phenotypic variance that are due to genetic and environmental influences. The simplest such decomposition (univariate polygenic analysis) is one where the additive genetic contribution of a single trait is indexed by its narrow-sense heritability, denoted by h^2. We first estimated the heritability of all traits. All inflammation measures were normalized using an inverse Gaussian transformation. For all traits, age, age^2, sex and their interactions, as well as BMI were entered as covariates into univariate polygenic models.

Under a bivariate polygenic model, the phenotypic covariance between each inflammation phenotype and suicide attempt is decomposed into its genetic and environmental constituents to determine the extent to which they are influenced by shared genetic effects. Bivariate polygenic analysis was applied to pairs of inflammation and suicide traits, with relevant covariates (those deemed significant in univariate analysis, see above) for each trait. We also ran the bivariate polygenic models with potentially confounding diagnoses as covariates including: any anxiety disorder, current and lifetime substance and alcohol dependence disorders, bipolar disorder type I and type II, schizoaffective disorder and schizophrenia.

We also applied a coefficient-of-relatedness-analysis to *lifetime suicide attempt* and each cytokine. Briefly, this analysis leverages the many coefficients of relationship that exist in extended-pedigree data. The coefficient of relationship refers to the average number of alleles held in common between individuals. The coefficient of relatedness refers to the average number of alleles held in common between individuals; for example, first-degree relatives (e.g. full siblings or parents) share on average 50% of their alleles, second-degree relatives (e.g. grandparents or aunts/uncles) share 25%, third-degree relatives (e.g. great-grandparents or great-aunts/-uncles) share 12.5%, and so on. Thus, it is possible, given an individual with a disease, to index all other pedigree members by their degree of relatedness to that individual. This scalar can then be used to perform a fixed-effect single-degree-of-freedom test within the univariate polygenic analysis framework (outlined above), providing an estimate of the standardized genetic covariance between the potential endophenotype and illness risk [61]. This analysis is useful because affected individuals are excluded and thus, confounding by factors such as medication status and alteration in inflammation levels as a consequence of suicide attempt is minimized.

To control for multiple testing of main effects, the false discovery rate (FDR) was set at 5% [62].

Results

Heritability of Risk for Suicide Attempt and Suicidal Ideation

Of the individuals assessed as part of GOBS, 159 endorsed having attempted suicide in their lifetime and 135 endorsed some level of current suicidal ideation. Of those individuals that had attempted suicide, 98 had a diagnosis of a past major depressive disorder. Table 1 provides descriptive statistics for these individuals. A greater proportion of females than

males had attempted suicide and were experiencing current suicidal ideation, but age and BMI were fairly consistent across groups (Table 1).

Table 2 shows results of univariate polygenic analysis, including covariate effects, on risk for suicide attempt and current suicidal ideation. Both suicide attempt ($h^2 = 0.46$, $p_{FDR} = 1.68 \times 10^{-4}$) and suicidal ideation ($h^2 = 0.47$, $p_{FDR} = 1.15 \times 10^{-03}$) were significantly heritable. Sex was a significant covariate of both suicide traits ($p = 0.01$ and $p = 0.04$, respectively) but neither age, nor age^2 (nor their interactions with sex), nor BMI were significant covariates of either suicide trait.

Heritability of Cytokines

The heritability estimates and covariate effects for the interleukin markers are shown in Table 2. TNF-α ($h^2 = 0.26$, $p_{FDR} = 3.11 \times 10^{-08}$), IL-6 ($h^2 = 0.18$, $p_{FDR} = 1.68 \times 10^{-04}$) and IL-8 ($h^2 = 0.30$, $p_{FDR} = 7.15 \times 10^{-13}$) were significantly heritable (Table 2) and were significantly associated with age. IL-8 and TNF-α were significantly associated with sex and Il-6 and TNF-α showed strong association with BMI.

Genetic Correlation between Cytokines with Risk for Lifetime Suicide Attempt and Current Suicidal Ideation

The results from bivariate polygenic analysis (including significant covariates from each trait according to univariate polygenic analysis, see above) applied to risk for *lifetime suicidal attempt* and *current suicidal ideation* paired with each cytokine marker are shown in Table 3. This analysis revealed that only IL-8 ($\rho_g = 0.49$, $se = 0.17$, $p_{FDR} = 8.94 \times 10^{-03}$) exhibited a significant genetic overlap with risk for *lifetime suicide attempt.* The genetic correlation between IL-8 and *current suicidal ideation* was not significant. Neither TNF-α nor IL-6 showed significant genetic correlation with risk for *lifetime suicide attempt* nor *current suicidal ideation.*

Figure 1 shows results of coefficient-of-relatedness analysis, which excluded affected individuals. While IL-8 ($\beta = 0.54$, $se = 0.15$, $p_{FDR} = 1.25 \times 10^{-03}$) levels varied as a function of genetic risk for suicide attempt, TNF-α ($\beta = 0.20$, $se = 0.15$, $p_{FDR} = 0.25$) and IL-6 ($\beta = 0.12$, $se = 0.05$, $p_{FDR} = 0.47$) levels did not (Figure 1). Altogether, these results suggest that IL-8, but not IL-6 or TNF-α, has genetic overlap with risk for suicide attempt, and also that IL-8, but not IL-6 or TNF-α, varies with genetic risk for suicide attempt in unaffected relatives. In sum, in this sample, IL-8 appears to be a better marker of suicide risk than IL-6.

The genetic correlations between the inflammatory markers were all significantly different from zero but also significantly different from 1 indicating partial genetic overlap with specificity between markers (Table S1).

Comorbid psychiatric diagnoses derived from the MINI as well as self-reported somatic medical conditions and self-reported current prescriptions are listed in Table S2 and Table S3. The genetic correlation between *lifetime suicide attempt* and IL-8 remained significant when those comorbid conditions (any alcohol or substance use disorder, bipolar disorder, psychosis, diabetes) that were significant covariates of either trait were included as covariates in the bivariate polygenic model ($\rho_g = 0.39$, $se = 0.19$, $p_{FDR} = 0.03$).

The genetic correlation between *lifetime suicide attempt* and IL-8 remained significant when currently prescribed medications (antidepressants, antidiabetics, ACE inhibitor, antipsychotics, diuretics, opioids) that were significant covariates of either trait were included as covariates in the bivariate polygenic model ($\rho_g = 0.48$, $se = 0.18$, $p_{FDR} = 7.13 \times 10^{-03}$).

The Effect of BMI on the Relationship Between Risk for Lifetime Suicide Attempt and IL-6

Given previous findings on IL-6 and suicide risk, it was surprising that IL-8, but not IL-6, demonstrated a significant genetic overlap with risk for *lifetime suicide attempt.* Since IL-6 was significantly associated with BMI, BMI (mean = 31.38, SD = 7.53, range = 15.53-78.37) was included as a covariate in the bivariate polygenic model between IL-6 and suicide attempt. Removing BMI as a covariate generated a significant genetic correlation ($\rho_g = 0.53$, se = 0.19, $p_{FDR} = 0.02$), suggesting that the effects of BMI should be carefully considered when investigating the relationship between inflammatory measures, particularly IL-6, and risk for suicide attempt. We also ran a trivariate model of IL-6, *lifetime suicide attempt* and BMI. Using this model we estimated the genetic correlations between pairs of traits in the same model rather than treating BMI as a confound or nuisance covariate. Inspection of Figure 2 shows that the genetic correlation between IL-6 and risk for lifetime suicide attempt was not significant when BMI was included as a third phenotype in the model.

Removing BMI as a covariate in the bivariate polygenic model between TNF-α and suicide attempt did not alter the non-significant genetic correlation between the trait pair ($\rho_g = 0.22$, se = 0.20, $p_{FDR} = 0.36$).

The Effect of Sex on the Relationship Between Lifetime Suicide Attempt and IL-8

Since both suicide attempt and IL-8 exhibited effects of sex (Table 2), we also ran the bivariate polygenic model between suicide attempt and IL-8 separately in males and females. In females, the genetic correlation between IL-8 and risk for suicide attempt was significant ($\rho_g = 0.56$, se = 0.21, $p_{FDR} = 0.02$), but not in males ($\rho_g = 0.27$, se = 0.86, $p_{FDR} = 0.36$). However, the heritability of risk for suicide attempt in the bivariate model was much lower in males ($h^2 = 0.11$, $se = 0.36$) than in females ($h^2 = 0.52$, $se = 0.17$). This may be because there is an insufficient number of cases in males for h^2 to be reliably estimated. To circumvent this limitation, we constrained the threshold of risk for suicide attempt in males to be the same as that in females (= 1.27), resulting in a heritability of risk for suicide attempt similar to that in females ($h^2 = 0.55$, $se = 0.37$). However, the genetic correlation remained non-significant ($\rho_g = 0.44$, se = 0.41, $p_{FDR} = 0.36$). These analyses suggest that the relationship between suicide attempt and IL-8 in this sample is moderated by the sex, such that the relationship is driven largely by females and is not evident in males. This finding implies a strong sex-specific effect for IL-8 on lifetime risk for suicide attempt.

Does Major Depressive Disorder (MDD) Confound the Relationship Between Lifetime Suicide Attempt and IL-8?

Of the 159 individuals that had attempted suicide, 98 (62%) also had a lifetime diagnosis of MDD, making it possible that MDD confounded the relationship between IL-8 and lifetime

suicide attempt. However, when the presence of any major depressive disorder was included as a covariate in the bivariate polygenic model the relationship between IL-8 and lifetime suicide attempt remained significant ($\rho_g = 0.48$, se $= 0.20$, $p_{FDR} = 0.02$). Moreover, in a trivariate model where the genetic correlations between trait pairs are estimated in the same model, the genetic correlation between risk for suicide attempt and IL-8 remained significant ($\rho_g = 0.48$, $p_{FDR} = 0.01$), the genetic correlation between risk for suicide attempt and MDD was also, unsurprisingly, significant ($\rho_g = 0.92$, $p_{FDR} = 3.00 \times 10^{-04}$), and the genetic correlation between risk for MDD and IL-8 was significant ($\rho_g = 0.40$, $p_{FDR} = 0.04$). Of the 112 females that had attempted suicide, 72 ($= 64\%$) had been diagnosed with MDD. Running the trivariate model in females alone generated similar results to those from the entire sample. The genetic correlation between suicide attempt and IL-8 was significant ($\rho_g = 0.52$, $p_{FDR} = 0.03$), as was the genetic correlation between suicide attempt and MDD ($\rho_g = 0.90$, $p_{FDR} = 1.92 \times 10\text{-}03$). However, the genetic correlation between IL-8 and MDD was not significant ($\rho_g = 0.42$, $p_{FDR} = 0.07$).

Discussion

There is clear evidence for inflammatory alterations in individuals who have engaged in suicidal behavior[6]. Using data from a large, multi-family, multi-generational sample we have advanced understanding of this relationship in several ways.

First, we tested the extent to which alterations in the inflammatory markers IL-6 and IL-8 shared a genetic overlap with risk for suicide attempt. Studies have already shown that suicide attempts are associated with increased inflammation [5,6]. However, no study has previously looked at whether this association is caused by the same genes affecting both traits, as opposed to environmental factors (e.g. inflammation levels increasing after a suicide attempt). We provide evidence that plasma-based IL-8 and risk for suicide attempt are driven, at least in part, by a common set of genes. This suggests that alterations in peripherally measured IL-8 do not arise merely as a consequence of suicidal behavior but that some of the same genes that affect inflammation levels also mediate risk for suicide attempt. That is, the biological mechanisms that regulate IL-8 are some of the same that impact risk for a suicide attempt. Future studies attempting to isolate genes that influence risk for suicide attempt might focus their attention on some of the well-characterized molecular pathways for IL-8 regulation.

Second, we tested whether the genetic overlap between IL-8 and risk for suicide attempt varied as a function of sex. In line with previous literature [30], both suicidal ideation and attempts were significantly more common in women than in men in the present sample. By stratifying our analyses by sex, we showed that a genetic correlation between IL-8 and risk for suicide attempt was present in both males and females but that, overall, the effect appeared to be driven by females. This finding suggests important differences in the pathophysiology of suicide attempts in males and females. Specifically, in females, but not necessarily in males, the biological mechanisms associated with IL-8 are a key contributor to risk for suicide. This finding is in line with evidence that the immune response, including the production of cytokines and chemokines, is strongly affected by sex [31], and that women are more susceptible than men to inflammation-induced mood symptoms [63]. Recent findings

showed that depressed males exhibited no differences in a range of serum-based pro-inflammatory markers compared to healthy controls, while depressed females showed higher levels on a number of markers, including IL-8 [64]. Our trivariate results in females showed that risk for suicide attempt, but not MDD, had shared genetic influences with IL-8, suggesting that suicidality, rather than other aspects of depressive symptomatology, drives the apparent relationship between MDD and inflammation. However, the non-significant genetic correlations between risk for suicide and MDD in females could also be due to a lack of power, particularly given that we observed separate and significant correlations in the larger sample. Future work might focus on what specifically drives these differences in males and females, for example the interaction between sex hormones, immune response, and suicidality [65,66].

Third, we investigated the extent to which BMI, as a proxy of adiposity, confounded the relationship between IL-6 and risk for suicide attempt. IL-6 has been described previously as one of the most reliable peripheral biomarkers of MDD [67-69]. IL-6 is more often studied, than for example IL-8, in relation to suicidality [6]. However, IL-6 is susceptible to a major confounder, adiposity, which is also often associated with disorders of mood [70,71]. Up to a third of circulating IL-6 originates from adipose tissue [42]. Indeed, in the present study, the relationship between risk for suicide attempt and IL-6 was confounded by BMI since the genetic correlation between IL-6 and suicide attempt was only significant when BMI was not included as a covariate. Of course, BMI is an imperfect proxy for adiposity because it cannot differentiate between muscle and fat [72]. Nevertheless, the present study suggests that BMI is an important source of bias in IL-6 levels and should be considered when assessing the association between IL-6 and suicide. This is not to say that BMI should be included as a covariate in all studies focusing on the relationship between mood and/or suicide and inflammation, however our results strongly suggest that the possibly influence of BMI on increased inflammation levels should be considered.

We showed that IL-8, but not IL-6 (when BMI was included as a covariate) or TNF-α, overlapped with risk for suicide attempt. This is intriguing since these are three belong to a diverse group of key communicators in the development of both acute and chronic inflammation [73], called cytokines. However, each also has distinct structural morphologies and roles [74]. IL-6 and TNF-α are members of pleiotropic cytokines with roles related to the maturation of B cells into anti-body producing plasma cells, T cell activation, B-lymphocyte function and haemtopoiesis [73,75,76]. Chemokines (or, chemotactic cytokines) are a family of small cytokines that include IL-8, whose primary role is to induce chemotaxis in local cells, recruiting leukocytes to the site of infection or injury [73]. Thus, the two interleukins have quite different roles in the inflammatory response; while IL-6 is a cytokine that initiates an inflammatory response by triggering signaling cascades, IL-8 is a chemokine that initiates cell movement to recruit immune cells to the site of infection. To the extent that IL-6 and IL-8 have different roles it makes sense that one, but not the other, might be involved in the pathophysiology of risk for suicide. However, further work is required to delineate how chemotaxis, particularly in the central nervous system, might increase risk for suicidal behavior.

Despite a wealth of research dedicated to the topic, few, if any, clinically translatable biomarkers have been identified in psychiatry [77]. This study provides strong support for IL-8 as a biomarker of risk for suicide attempt. Recent national increases in suicidal behavior[3], combined with the poor predictive power of traditional clinical risk factors [78], mean that the need for robust markers of suicidal behavior has never been greater. This is particularly true when one considers that 54% of individuals who died by suicide in 2016 had no diagnosed mental illness [1]. IL-8 is already in routine use as a marker in various medical subspecialties for a number of clinical conditions, including prostatitis, non-Hodgkin's lymphoma, bladder cancer, pulmonary infections and others [79]). Our findings suggest that IL-8 might also have utility in psychiatry, particularly in the detection of suicidal intent.

The heritability of TNF-α, IL-6 and IL-8 have been published previously. Heritability estimates of IL-6 from twin studies range between 0.17 and 0.61, though the majority of studies indicate estimates closer to 0.61[25,26,80-83]. The classical twin design has been criticized for giving upwardly biased heritability estimates {[84-86]. Indeed, a large extended pedigree study indicated that the heritability of IL-6 was 0.25, which is somewhat closer to the heritability found in the present study [87]. Moreover, one of the twin studies that accounted for BMI in their models, as we did in the present study, showed that the heritability of IL=6 was 0.26 [26]. TNF-α and IL-8 have featured less prominently in heritability studies of inflammatory traits. The heritability of TNF-α has been estimated between 0.26 and 0.53 [25,26]. Only one study has, to the best our knowledge, investigated the heritability of IL-8 in humans prior to the present one and that estimated heritability of IL-8 to be 1.00 [27]. The authors of that study acknowledge that the high heritability of IL-8 might be due to an unapparent infection running in families or possibly due to medication effects. Pedigree-based analyses in cows and baboons indicate that the heritability of IL-8 is 0.30 and 0.28 respectively [88,89]. Thus, in general the heritability of cytokines vary considerably in the literature which is likely due to the variety of research designs and inflammation assays employed. However, the estimates given in the present study fall within the limits of those published previously.

The present study has a number of limitations that might be addressed by future work. First, personality traits such as impulsivity or aggressiveness might confound or even mediate the relationship between inflammation and suicide attempt. Impulsivity and aggression have been cited as essential features of suicidal behavior [90,91]. Moreover, impulsivity and suicide attempt via a violent method are related to plasma-based IL-6 [39]. Second, the participants in the present study are of Mexican American ancestry and it is possible that the results we observe here are population specific. Subsequent work should focus on replicating our results in other ethnicities. Third, increased circulating cytokine levels have been observed in response to stress [92], infection [93], trauma [94], arthritis [95,96], psoriasis [97], atherosclerosis [98] and obesity [99]. While we accounted for BMI other confounds were not accounted for, which might have affected our heritability (and by extension genetic correlation) estimates. Fourth, as authors of previous studies have noted common environmental influences, e.g. an unapparent infection running in a family, might increase inflammation and confound estimates of heritability (and by extension genetic correlations) [27], however the families in question were nuclear families. The present study, on the other hand, used an extended pedigree design. It is a widely held view among genetics researchers that one of the benefits

of extended pedigrees relative to smaller families is that there is reduced confounding of genetic and shared environmental effects because family members are usually distributed across multiple households [100]. Where in the present study the largest family comprised 178 individuals (mean size = 21.67) it is highly unlikely that entire pedigrees were subject to such common environmental effects. Fifth, inflammation levels vary diurnally [101]. While in the present study all blood draws were completed within a narrow time window in the morning. Future work that might focus on tracking whether inflammation levels track with suicidal ideation, which are subject to change over a matter of hours [102,103]. This would be an advancement of the current study, which used a relatively crude index of suicide assessment.

It is not possible, in the present study, to draw causal inference from our results due to the cross-sectional nature of the study. Although, we found evidence for a strong and significant genetic correlation between risk for suicide attempt and IL-8 levels. A genetic correlation, in contrast to a phenotypic correlation, implies that both traits are influenced by partially overlapping genetic factors: here, directionality is of course guaranteed (genes caused the correlation between the traits). Causal evidence for the association between inflammation and depression has been provided by experiments using exogenously-induced inflammation [104,105]. After exposure to rhinovirus or influenza those individuals that became infected showed increase in IL-6 production that was associated with reduced positive (but not increased negative) affect [106]. The introduction of an endotoxin (*Salmonella abortus equi*) and concomitant increases in inflammatory markers was associated with increased sleepiness [107] and also depressed mood [108]. Administration of the *Salmonella typhi* vaccine and associated increases in IL-6 resulted in increased negative mood [109]. Increases in IL-6 after receiving the influenza vaccine were associated with increases in depressed mood (though not with decreases in positive affect or increases in fatigue [110]. However, few studies have focused on suicidality using these paradigms and subsequent work might focus on this.

In the present study, IL-8, but not IL-6, showed shared genetic influences with risk for suicide attempt. This genetic overlap appeared to be particularly pronounced in females, providing strong evidence for a sex-specific effect whereby the same biologic mechanisms that drive IL-8 production and metabolism also drive, at least to a certain extent, suicide attempts in women. Moreover, based on the results of this study, the effect of BMI on inflammation levels may have confounded results from previous studies that placed greater emphasis on IL-6 for suicide risk. These findings represents a significant advancement in knowledge by demonstrating that inflammation alterations are not simply a secondary manifestation of suicidal behavior, but rather, the pathophysiology of suicide attempts is, at least partly, underpinned by the same biological mechanisms responsible for regulating inflammatory response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Stone DM, Simon TR, Fowler KA, et al. Vital signs: Trends in state suicide rates — united states, 1999–2016 and circumstances contributing to suicide — 27 states, 2015. Morbidity and Morality Weekly Report. 2018;67(22):617–624.

2. Brundin L, Bryleva EY, Thirtamara Rajamani K. Role of inflammation in suicide: From mechanisms to treatment. Neuropsychopharmacology. 2017;42(l):271–283. doi: 10.1038/npp.2016.116 [doi], [PubMed: 27377015]

3. Bertolote JM, Fleischmann A, De Leo D, et al. Repetition of suicide attempts: Data from emergency care settings in five culturally different low- and middle-income countries participating in the WHO SUPRE-MISS study. Crisis. 2010;31(4):194–201. doi: 10.1027/0027-5910/a000052 [doi], [PubMed: 20801749]

4. Strimbu K, Tavel JA. What are biomarkers? Curr Opin HIV AIDS. 2010;5(6):463–466. doi: 10.1097/COH.0b013e32833ed177 [doi], [PubMed: 20978388]

5. Black C, Miller BJ. Meta-analysis of cytokines and chemokines in suicidality: Distinguishing suicidal versus nonsuicidal patients. Biol Psychiatry. 2015;78(l):28–37. doi: S0006-3223(14)00794-X [pii], [PubMed: 25541493]

6. Brundin L, Bryleva EY, Thirtamara Rajamani K. Role of inflammation in suicide: From mechanisms to treatment. Neuropsychopharmacology. 2017;42(l):271–283. doi: 10.1038/npp.2016.116 [doi], [PubMed: 27377015]

7. Coccaro EF. Association of C-reactive protein elevation with trait aggression and hostility in personality disordered subjects: A pilot study. J Psychiatr Res. 2006;40(5):460–465. doi: S0022-3956(05)00053-l [pii]. [PubMed: 15993896]

8. Clark SM, Pocivavsek A, Nicholson JD, et al. Reduced kynurenine pathway metabolism and cytokine expression in the prefrontal cortex of depressed individuals. J Psychiatry Neurosci. 2016;41(6):386–394. doi: 10.1503/jpn.150226 [pii]. [PubMed: 27070351]

9. Janelidze S, Suchankova P, Ekman A, et al. Low IL-8 is associated with anxiety in suicidal patients: Genetic variation and decreased protein levels. Acta Psychiatr Scand. 2015;131(4):269–278. doi: 10.1111/acps.l2339 [doi], [PubMed: 25251027]

10. Pandey GN, Rizavi HS, Ren X, et al. Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. J Psychiatr Res. 2012;46(l):57–63. doi: 10.1016/j.jpsychires.2011.08.006 [doi], [PubMed: 21906753]

11. Isung J, Aeinehband S, Mobarrez F, et al. Low vascular endothelial growth factor and interleukin-8 in cerebrospinal fluid of suicide attempters. Transl Psychiatry. 2012;2:el96. doi: 10.1038/tp.2012.123 [doi],

12. Janelidze S, Mattel D, Westrin A, Traskman-Bendz L, Brundin L. Cytokine levels in the blood may distinguish suicide attempters from depressed patients. Brain Behav Immun. 2011;25(2):335–339. doi: 10.1016/j.bbi.2010.10.010 [doi], [PubMed: 20951793]

13. Lindqvist D, Janelidze S, Hagell P, et al. Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. Biol Psychiatry. 2009;66(3):287–292. doi: 10.1016/j.biopsych.2009.01.030 [doi], [PubMed: 19268915]

14. Gabbay V, Klein RG, Guttman LE, et al. A preliminary study of cytokines in suicidal and nonsuicidal adolescents with major depression. J Child Adolesc Psychopharmacol. 2009;19(4):423–430. doi: 10.1089/cap.2008.0140 [doi]. [PubMed: 19702494]

15. Tonelli LH, Stiller J, Rujescu D, et al. Elevated cytokine expression in the orbitofrontal cortex of victims of suicide. Acta Psychiatr Scand. 2008;117(3):198–206. doi: ACP1128 [pii]. [PubMed: 18081924]

16. Steiner J, Bielau H, Brisch R, et al. Immunological aspects in the neurobiology of suicide: Elevated microglial density in schizophrenia and depression is associated with suicide. J Psychiatr Res. 2008;42(2):151–157. doi: S0022-3956(06)00218-4 [pii]. [PubMed: 17174336]

17. Nassberger L, Traskman-Bendz L. Increased soluble interleukin-2 receptor concentrations in suicide attempters. Acta Psychiatr Scand. 1993;88(1):48–52. [PubMed: 8372695]

18. Steiner J, Walter M, Gos T, et al. Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: Evidence for an immune-modulated glutamatergic neurotransmission? J Neuroinflammation. 2011;8:94–2094-8-94. doi: 10.1186/1742-2094-8-94 [doi]. [PubMed: 21831269]

19. Pandey GN, Rizavi HS, Ren X, Bhaumik R, Dwivedi Y. Toll-like receptors in the depressed and suicide brain. J Psychiatr Res. 2014;53:62–68. doi: 10.1016/j.jpsychires.2014.01.021 [doi]. [PubMed: 24565447]

20. Schnieder TP, Trencevska I, Rosoklija G, et al. Microglia of prefrontal white matter in suicide. J Neuropathol Exp Neurol. 2014;73(9):880–890. doi: 10.1097/NEN.0000000000000107 [doi]. [PubMed: 25101704]

21. Torres-Platas SG, Cruceanu C, Chen GG, Turecki G, Mechawar N. Evidence for increased microglial priming and macrophage recruitment in the dorsal anterior cingulate white matter of depressed suicides. Brain Behav Immun. 2014;42:50–59. doi: 10.1016/j.bbi.2014.05.007 [doi]. [PubMed: 24858659]

22. Busse M, Busse S, Myint AM, et al. Decreased quinolinic acid in the hippocampus of depressive patients: Evidence for local anti-inflammatory and neuroprotective responses? Eur Arch Psychiatry Clin Neurosci. 2015;265(4):321–329. doi: 10.1007/s00406-014-0562-0 [doi]. [PubMed: 25409655]

23. O'Donovan A, Rush G, Hoatam G, et al. Suicidal ideation is associated with elevated inflammation in patients with major depressive disorder. Depress Anxiety. 2013;30(4):307–314. doi: 10.1002/da.22087 [doi]. [PubMed: 23504697]

24. Zai CC, de Luca V, Strauss J, Tong RP, Sakinofsky I, Kennedy JL. Genetic factors and suicidal behavior In: Dwivedi Y, ed. The neurobiological basis of suicide. Boca Raton, FL: CRC Press; 2012:213–254.

25. de Craen AJ, Posthuma D, Remarque EJ, van den Biggelaar AH, Westendorp RG, Boomsma DI. Heritability estimates of innate immunity: An extended twin study. Genes Immun. 2005;6(2):167–170. doi: 6364162 [pii]. [PubMed: 15674372]

26. Amaral WZ, Krueger RF, Ryff CD, Coe CL. Genetic and environmental determinants of population variation in interleukin-6, its soluble receptor and C-reactive protein: Insights from identical and fraternal twins. Brain Behav Immun. 2015;49:171–181. doi: 10.1016/j.bbi.2015.05.010 [doi]. [PubMed: 26086344]

27. Sargurupremraj M, Pukelsheim K, Hofer T, Wjst M. Intermediary quantitative traits--an alternative in the identification of disease genes in asthma? Genes Immun. 2014;15(1):1–7. doi: 10.1038/gene.2013.53 [doi]. [PubMed: 24131956]

28. Rainville JR, Hodes GE. Inflaming sex differences in mood disorders. Neuropsychopharmacology. 2018. doi: 10.1038/s41386-018-0124-7 [doi].

29. Hedegaard H, Curtin SC, Warner M. Suicide rates in the united states continue to increase. https://www.cdc.gov/nchs/data/databriefs/db309.pdf. Updated 2018 Accessed 09/27, 2018.

30. Canetto SS, Sakinofsky I. The gender paradox in suicide. Suicide Life Threat Behav. 1998;28(1):1–23. [PubMed: 9560163]

31. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016;16(10):626–638. doi: 10.1038/nri.2016.90 [doi]. [PubMed: 27546235]

32. Bouman A, Heineman MJ, Faas MM. Sex hormones and the immune response in humans. Hum Reprod Update. 2005;11(4):411–423. doi: dmi008 [pii]. [PubMed: 15817524]

33. Nalbandian G, Kovats S. Understanding sex biases in immunity: Effects of estrogen on the differentiation and function of antigen-presenting cells. Immunol Res. 2005;31(2):91–106. doi: IR:31:2:091 [pii]. [PubMed: 15778508]

34. Whitacre CC. Sex differences in autoimmune disease. Nat Immunol. 2001;2(9):777–780. doi: 10.1038/ni0901-777 [doi]. [PubMed: 11526384]

35. Tonelli LH, Stiller J, Rujescu D, et al. Elevated cytokine expression in the orbitofrontal cortex of victims of suicide. Acta Psychiatr Scand. 2008;117(3):198–206. doi: ACP1128 [pii]. [PubMed: 18081924]

36. Pandey GN, Rizavi HS, Ren X, et al. Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. J Psychiatr Res. 2012;46(1):57–63. doi: 10.1016/j.jpsychires.2011.08.006 [doi]. [PubMed: 21906753]

37. Erhardt S, Lim CK, Linderholm KR, et al. Connecting inflammation with glutamate agonism in suicidality. Neuropsychopharmacology. 2013;38(5):743–752. doi: 10.1038/npp.2012.248 [doi]. [PubMed: 23299933]

38. Coccaro EF, Lee R, Coussons-Read M. Elevated plasma inflammatory markers in individuals with intermittent explosive disorder and correlation with aggression in humans. JAMA Psychiatry. 2014;71(2):158–165. doi: 10.1001/jamapsychiatry.2013.3297 [doi]. [PubMed: 24352431]

39. Isung J, Aeinehband S, Mobarrez F, et al. High interleukin-6 and impulsivity: Determining the role of endophenotypes in attempted suicide. Transl Psychiatry. 2014;4:e470. doi: 10.1038/tp.2014.113 [doi]. [PubMed: 25335166]

40. Schneider TP, Trencevska I, Rosoklija G, et al. Microglia of prefrontal white matter in suicide. J Neuropathol Exp Neurol. 2014;73(9):880–890. doi: 10.1097/NEN.0000000000000107 [doi]. [PubMed: 25101704]

41. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860–867. doi: nature05485 [pii]. [PubMed: 17167474]

42. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: Is interleukin-6 the link? Atherosclerosis. 2000;148(2):209–214. doi: S0021-9150(99)00463-3 [pii]. [PubMed: 10657556]

43. Mohamed-Ali V, Goodrick S, Rawesh A, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J Clin Endocrinol Metab. 1997;82(12):4196–4200. doi: 10.1210/jcem.82.12.4450 [doi]. [PubMed: 9398739]

44. Amaral WZ, Krueger RF, Ryff CD, Coe CL. Genetic and environmental determinants of population variation in interleukin-6, its soluble receptor and C-reactive protein: Insights from identical and fraternal twins. Brain Behav Immun. 2015;49:171–181. doi: 10.1016/j.bbi.2015.05.010 [doi]. [PubMed: 26086344]

45. Perera S, Eisen R, Bawor M, et al. Association between body mass index and suicidal behaviors: A systematic review protocol. Syst Rev. 2015;4:52–015–0038-y. doi: 10.1186/s13643-015-0038-y [doi]. [PubMed: 25927506]

46. Magnusson PK, Rasmussen F, Lawlor DA, Tynelius P, Gunnell D. Association of body mass index with suicide mortality: A prospective cohort study of more than one million men. Am J Epidemiol. 2006;163(1):1–8. doi: kwj002 [pii]. [PubMed: 16269577]

47. Kaplan MS, McFarland BH, Huguet N. The relationship of body weight to suicide risk among men and women: Results from the US national health interview survey linked mortality file. J Nerv Ment Dis. 2007;195(11):948–951. doi: 10.1097/NMD.0b013e3181594833 [doi]. [PubMed: 18000458]

48. Mukamal KJ, Rimm EB, Kawachi I, O'Reilly EJ, Calle EE, Miller M. Body mass index and risk of suicide among one million US adults. Epidemiology. 2010;21(1):82–86. doi: 10.1097/EDE.0b013e3181c1fa2d [doi]. [PubMed: 19907331]

49. Gao S, Juhaeri J, Reshef S, Dai WS. Association between body mass index and suicide, and suicide attempt among british adults: The health improvement network database. Obesity (Silver Spring). 2013;21(3):E334–42. doi: 10.1002/oby.20143 [doi]. [PubMed: 23592687]

50. Osler M, Nybo Andersen AM, Nordentoft M. Impaired childhood development and suicidal behaviour in a cohort of danish men born in 1953. J Epidemiol Community Health. 2008;62(1):23–28. doi: 62/1/23 [pii]. [PubMed: 18079329]

51. Carpenter KM, Hasin DS, Allison DB, Faith MS. Relationships between obesity and DSM-IV major depressive disorder, suicide ideation, and suicide attempts: Results from a general population study. Am J Public Health. 2000;90(2):251–257. [PubMed: 10667187]

52. Schneider B, Lukaschek K, Baumert J, Meisinger C, Erazo N, Ladwig KH. Living alone, obesity, and smoking increase risk for suicide independently of depressive mood findings from the

population-based MONICA/KORA augsburg cohort study. J Affect Disord. 2014;152–154:416-421. doi: 10.1016/j.jad.2013.10.007 [doi]. [PubMed: 25618002]

53. Elovainio M, Shipley MJ, Ferrie JE, et al. Obesity, unexplained weight loss and suicide: The original whitehall study. J Affect Disord. 2009;116(3):218–221. doi: 10.1016/j.jad.2008.12.002 [doi]. [PubMed: 19097646]

54. Lester D, Iliceto P, Pompili M, Girardi P. Depression and suicidality in obese patients. Psychol Rep. 2011;108(2):367–368. doi: 10.2466/06.09.12.15.PR0.108.2.367-368 [doi]. [PubMed: 21675551]

55. Wagner B, Klinitzke G, Brahler E, Kersting A. Extreme obesity is associated with suicidal behavior and suicide attempts in adults: Results of a population-based representative sample. Depress Anxiety. 2013;30(10):975–981. doi: 10.1002/da.22105 [doi]. [PubMed: 23576272]

56. Wagner B, Klinitzke G, Brahler E, Kersting A. Extreme obesity is associated with suicidal behavior and suicide attempts in adults: Results of a population-based representative sample. Depress Anxiety. 2013;30(10):975–981. doi: 10.1002/da.22105 [doi]. [PubMed: 23576272]

57. Sublette ME, Galfalvy HC, Fuchs D, et al. Plasma kynurenine levels are elevated in suicide attempters with major depressive disorder. Brain Behav Immun. 2011;25(6):1272–1278. doi: 10.1016/j.bbi.2011.05.002 [doi]. [PubMed: 21605657]

58. Olvera RL, Bearden CE, Velligan DI, et al. Common genetic influences on depression, alcohol, and substance use disorders in mexican-american families. Am J Med Genet B Neuropsychiatr Genet. 2011;156B(5):561–568. doi: 10.1002/ajmg.b.31196 [doi]. [PubMed: 21557468]

59. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The mini-international neuropsychiatric interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22–33;quiz 34–57.

60. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. Am J Hum Genet. 1998;62(5):1198–1211. doi: 10.1086/301844. [PubMed: 9545414]

61. Glahn DC, Williams JT, McKay DR, et al. Discovering schizophrenia endophenotypes in randomly ascertained pedigrees. Biol Psychiatry. 2015;77(1):75–83. doi: 10.1016/j.biopsych.2014.06.027 [doi]. [PubMed: 25168609]

62. Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. Annals of statistics. 2001;29(4):1165–1188.

63. Derry HM, Padin AC, Kuo JL, Hughes S, Kiecolt-Glaser JK. Sex differences in depression: Does inflammation play a role? Curr Psychiatry Rep. 2015;17(10):78-015–0618-5. doi: 10.1007/s11920-015-0618-5 [doi]. [PubMed: 26272539]

64. Birur B, Amrock EM, Shelton RC, Li L. Sex differences in the peripheral immune system in patients with depression. Front Psychiatry. 2017;8:108. doi: 10.3389/fpsyt.2017.00108 [doi]. [PubMed: 28670290]

65. Bouman A, Heineman MJ, Faas MM. Sex hormones and the immune response in humans. Hum Reprod Update. 2005;11(4):411–423. doi: dmi008 [pii]. [PubMed: 15817524]

66. Bouman A, Schipper M, Heineman MJ, Faas MM. Gender difference in the non-specific and specific immune response in humans. Am J Reprod Immunol. 2004;52(1):19–26. doi: 10.1111/j.1600-0897.2004.00177.x [doi]. [PubMed: 15214938]

67. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. Biol Psychiatry. 2009;65(9):732–741. doi: 10.1016/j.biopsych.2008.11.029 [doi]. [PubMed: 19150053]

68. Zorrilla EP, Luborsky L, McKay JR, et al. The relationship of depression and stressors to immunological assays: A meta-analytic review. Brain Behav Immun. 2001;15(3):199–226. doi: 10.1006/brbi.2000.0597 [doi]. [PubMed: 11566046]

69. Mossner R, Mikova O, Koutsilieri E, et al. Consensus paper of the WFSBP task force on biological markers: Biological markers in depression. World J Biol Psychiatry. 2007;8(3):141–174. doi: 780599961 [pii]. [PubMed: 17654407]

70. Shelton RC, Falola M, Li L, Zajecka J, Fava M, Papakostas GI. The pro-inflammatory profile of depressed patients is (partly) related to obesity. J Psychiatr Res. 2015;70:91–97. doi: 10.1016/j.jpsychires.2015.09.001 [doi]. [PubMed: 26424427]

71. Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA. Clinical depression and inflammatory risk markers for coronary heart disease. Am J Cardiol. 2002;90(12):1279–1283. doi: S0002914902028631 [pii]. [PubMed: 12480034]

72. Cornier MA, Despres JP, Davis N, et al. Assessing adiposity: A scientific statement from the american heart association. Circulation. 2011;124(18):1996–2019. doi: 10.1161/ CIR.0b013e318233bc6a [doi]. [PubMed: 21947291]

73. Turner MD, Nedjai B, Hurst T, Pennington DJ. Cytokines and chemokines: At the crossroads of cell signalling and inflammatory disease. Biochim Biophys Acta. 2014;1843(11):2563–2582. doi: S0167-4889(14)00196-7 [pii]. [PubMed: 24892271]

74. Ramesh G, MacLean AG, Philipp MT. Cytokines and chemokines at the crossroads of neuroinflammation, neurodegeneration, and neuropathic pain. Mediators Inflamm. 2013;2013:480739. doi: 10.1155/2013/480739 [doi]. [PubMed: 23997430]

75. Rieckmann P, Tuscano JM, Kehrl JH. Tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) in B-lymphocyte function. Methods. 1997;11(1):128–132. doi: S1046-2023(96)90396-5 [pii]. [PubMed: 8990098]

76. Kishimoto T IL-6: From its discovery to clinical applications. Int Immunol. 2010;22(5):347–352. doi: 10.1093/intimm/dxq030 [doi]. [PubMed: 20410258]

77. Venkatasubramanian G, Keshavan MS. Biomarkers in psychiatry - A critique. Ann Neurosci. 2016;23(1):3–5. doi: 10.1159/000443549 [doi]. [PubMed: 27536015]

78. Costanza A, D'Orta I, Perroud N, et al. Neurobiology of suicide: Do biomarkers exist? Int J Legal Med. 2014;128(1):73–82. doi: 10.1007/s00414-013-0835-6 [doi]. [PubMed: 23430141]

79. Shahzad A, Knapp M, Lang I, Kohler G. Interleukin 8 (IL-8) - a universal biomarker? Int Arch Med. 2010;3:11–7682-3-11. doi: 10.1186/1755-7682-3-11 [doi]. [PubMed: 20550702]

80. Worns MA, Victor A, Galle PR, Hohler T. Genetic and environmental contributions to plasma C-reactive protein and interleukin-6 levels--a study in twins. Genes Immun. 2006;7(7):600–605. doi: 6364330 [pii]. [PubMed: 16900203]

81. Pantsulaia I, Trofimov S, Kobyliansky E, Livshits G. Genetic and environmental influences on IL-6 and TNF-alpha plasma levels in apparently healthy general population. Cytokine. 2002;19(3):138–146. doi: S1043466602919599 [pii]. [PubMed: 12242080]

82. de Maat MP, Bladbjerg EM, Hjelmborg J, Bathum L, Jespersen J, Christensen K. Genetic influence on inflammation variables in the elderly. Arterioscler Thromb Vasc Biol. 2004;24(11):2168–2173. doi: 10.1161/01.ATV.0000143856.01669.e7 [doi]. [PubMed: 15345506]

83. Posthuma D, Meulenbelt I, de Craen AJ, et al. Human cytokine response to ex vivo amyloid-beta stimulation is mediated by genetic factors. Twin Res Hum Genet. 2005;8(2):132–137. doi: 10.1375/1832427053738728 [doi]. [PubMed: 15901476]

84. Joseph J Twin studies in psychiatry and psychology: Science or pseudoscience? Psychiatr Q. 2002;73(1):71–82. [PubMed: 11780600]

85. Kendler KS, Ohlsson H, Edwards AC, Lichtenstein P, Sundquist K, Sundquist J. A novel sibling-based design to quantify genetic and shared environmental effects: Application to drug abuse, alcohol use disorder and criminal behavior. Psychol Med. 2016;46(8):1639–1650. doi: 10.1017/ S003329171500224X [doi]. [PubMed: 26996079]

86. Benchek PH, Morris NJ. How meaningful are heritability estimates of liability? Hum Genet. 2013;132(12):1351–1360. doi: 10.1007/s00439-013-1334-z [doi]. [PubMed: 23867980]

87. Dupuis J, Larson MG, Vasan RS, et al. Genome scan of systemic biomarkers of vascular inflammation in the framingham heart study: Evidence for susceptibility loci on 1q. Atherosclerosis. 2005;182(2):307–314. doi: S0021-9150(05)00129-2 [pii]. [PubMed: 16159603]

88. Cockrum RR, Speidel SE, Salak-Johnson JL, et al. Genetic parameters estimated at receiving for circulating cortisol, immunoglobulin G, interleukin 8, and incidence of bovine respiratory disease in feedlot beef steers. J Anim Sci. 2016;94(7):2770–2778. doi: 10.2527/jas.2015-0222 [doi]. [PubMed: 27482664]

89. Rainwater DL, Shi Q, Mahaney MC, Hodara V, Vandeberg JL, Wang XL. Genetic regulation of endothelial inflammatory responses in baboons. Arterioscler Thromb Vasc Biol. 2010;30(8):1628–1633. doi: 10.1161/ATVBAHA.110.205740 [doi]. [PubMed: 20508207]

90. Corruble E, Damy C, Guelfi JD. Impulsivity: A relevant dimension in depression regarding suicide attempts? J Affect Disord. 1999;53(3):211–215. doi: S016503279800130X [pii]. [PubMed: 10404706]

91. Mann JJ, Arango VA, Avenevoli S, et al. Candidate endophenotypes for genetic studies of suicidal behavior. Biol Psychiatry. 2009;65(7):556–563. doi: 10.1016/j.biopsych.2008.11.021 [doi]. [PubMed: 19201395]

92. Heinz A, Hermann D, Smolka MN, et al. Effects of acute psychological stress on adhesion molecules, interleukins and sex hormones: Implications for coronary heart disease. Psychopharmacology (Berl). 2003;165(2):111–117. doi: 10.1007/s00213-002-1244-6 [doi]. [PubMed: 12417965]

93. Ng PC, Li K, Wong RP, et al. Proinflammatory and anti-inflammatory cytokine responses in preterm infants with systemic infections. Arch Dis Child Fetal Neonatal Ed. 2003;88(3):F209–13. [PubMed: 12719394]

94. Guo Y, Dickerson C, Chrest FJ, Adler WH, Munster AM, Winchurch RA. Increased levels of circulating interleukin 6 in burn patients. Clin Immunol Immunopathol. 1990;54(3):361–371. [PubMed: 2406054]

95. Uson J, Balsa A, Pascual-Salcedo D, et al. Soluble interleukin 6 (IL-6) receptor and IL-6 levels in serum and synovial fluid of patients with different arthropathies. J Rheumatol. 1997;24(11):2069–2075. [PubMed: 9375862]

96. Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and castleman disease. Blood. 2008;112(10):3959–3964. doi: 10.1182/blood-2008-05-155846 [doi]. [PubMed: 18784373]

97. Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. Mediators Inflamm. 2005;2005(5):273–279. doi: S0962935105507075 [pii]. [PubMed: 16258194]

98. Mendall MA, Patel P, Asante M, et al. Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. Heart. 1997;78(3):273–277. [PubMed: 9391290]

99. Park HS, Park JY, Yu R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6. Diabetes Res Clin Pract. 2005;69(1):29–35. doi: S0168-8227(04)00374-2 [pii]. [PubMed: 15955385]

100. Docherty AR, Kremen WS, Panizzon MS, et al. Comparison of twin and extended pedigree designs for obtaining heritability estimates. Behav Genet. 2015;45(4):461–466. doi: 10.1007/s10519-015-9720-z [doi]. [PubMed: 25894926]

101. Nilsonne G, Lekander M, Akerstedt T, Axelsson J, Ingre M. Diurnal variation of circulating interleukin-6 in humans: A meta-analysis. PLoS One. 2016;11(11):e0165799. doi: 10.1371/journal.pone.0165799 [doi]. [PubMed: 27832117]

102. Kleiman EM, Nock MK. Real-time assessment of suicidal thoughts and behaviors. Curr Opin Psychol. 2018;22:33–37. doi: S2352-250X(17)30163-X [pii]. [PubMed: 30122275]

103. Kleiman EM, Turner BJ, Fedor S, Beale EE, Huffman JC, Nock MK. Examination of real-time fluctuations in suicidal ideation and its risk factors: Results from two ecological momentary assessment studies. J Abnorm Psychol. 2017;126(6):726–738. doi: 10.1037/abn0000273 [doi]. [PubMed: 28481571]

104. DellaGioia N, Hannestad J. A critical review of human endotoxin administration as an experimental paradigm of depression. Neurosci Biobehav Rev. 2010;34(1):130–143. doi: 10.1016/j.neubiorev.2009.07.014 [doi]. [PubMed: 19666048]

105. Dooley LN, Kuhlman KR, Robles TF, Eisenberger NI, Craske MG, Bower JE. The role of inflammation in core features of depression: Insights from paradigms using exogenously-induced inflammation. Neurosci Biobehav Rev. 2018;94:219–237. doi: S0149-7634(18)30216-1 [pii]. [PubMed: 30201219]

106. Janicki-Deverts D, Cohen S, Doyle WJ, Turner RB, Treanor JJ. Infection-induced proinflammatory cytokines are associated with decreases in positive affect, but not increases in

negative affect. Brain Behav Immun. 2007;21(3):301–307. doi: S0889-1591(06)00301-1 [pii]. [PubMed: 17055218]

107. Hermann DM, Mullington J, Hinze-Selch D, Schreiber W, Galanos C, Pollmacher T. Endotoxin-induced changes in sleep and sleepiness during the day. Psychoneuroendocrinology. 1998;23(5):427–437. doi: S0306453098000304 [pii]. [PubMed: 9802118]

108. Reichenberg A, Yirmiya R, Schuld A, et al. Cytokine-associated emotional and cognitive disturbances in humans. Arch Gen Psychiatry. 2001;58(5):445–452. doi: yoa20072 [pii]. [PubMed: 11343523]

109. Wright CE, Strike PC, Brydon L, Steptoe A. Acute inflammation and negative mood: Mediation by cytokine activation. Brain Behav Immun. 2005;19(4):345–350. doi: S0889-1591(04)00133-3 [pii]. [PubMed: 15944074]

110. Kuhlman KR, Robles TF, Dooley LN, Boyle CC, Haydon MD, Bower JE. Within-subject associations between inflammation and features of depression: Using the flu vaccine as a mild inflammatory stimulus. Brain Behav Immun. 2018;69:540–547. doi: S0889-1591(18)30013-8 [pii]. [PubMed: 29458196]

Highlights

- IL-8 level and risk for suicide attempt are driven by a common set of genes

- The genetic correlation, derived via multivariate variance components methods. between IL-8 and suicide attempt was driven by females

- BMI is an important source of bias in IL-6 levels

- BMI should be considered when assessing the association between IL-6 and suicide

- Pathophysiology of suicide attempts is underpinned by the same biological mechanisms responsible for regulating inflammatory response
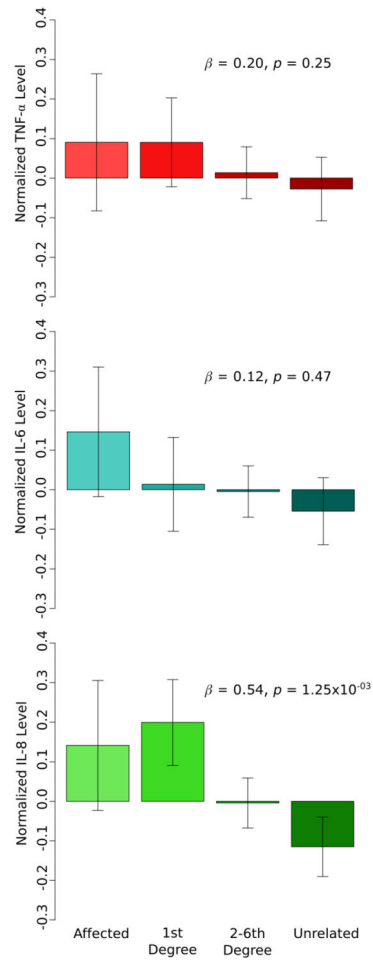
Figure 1.
Average levels of IL-6 and IL-8 in suicide attempters, unaffected relatives, and unaffected unrelateds.
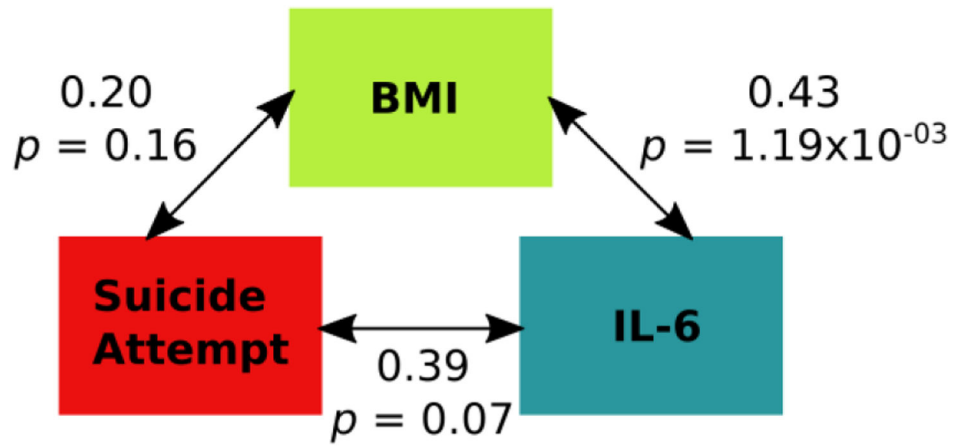
Figure 2.
Trivariate polygenic model of IL-6, BMI and lifetime suicide attempt.

Table 1.

Descriptive statistics (N, % female, mean age and BMI) of those individuals that have attempted suicide and those individuals that have current suicidal ideation.

Phenotype	Endorsement	N	% Female	Age (SD)	BMI (SD)
Suicide Attempt	Yes	159	70.44	41.09 (13.45)	32.65 (7.72)
	No	1725	58.72	42.23 (15.93)	31.57 (7.49)
Current Suicidal Ideation	Yes	135	74.07	42.73 (16.92)	31.42 (7.80)
	No	1749	58.60	42.09 (15.65)	31.67 (7.50)

Table 2.

Univariate polygenic analysis results for risk for suicide attempt and current suicidal ideation and inflammatory markers, including h^2 (and standard error) estimates, p-values and X^2 (and p-values) for covariates. Significant covariates are highlighted in **bold**.

Trait	h^2 (se)	p	age	ag^2	sex	age*sex	age^2*sex	BMI
Suicide Attempt	0.47 (0.13)	2.68×10^{-05}	0.61 (0.43)	0.74 (0.39)	**6.33 (0.01)**	0.87 (0.35)	0.42 (0.51)	1.03 (0.31)
Suicidal Ideation	0.46 (0.16)	2.75×10^{-04}	0.64 (0.42)	0.01 (0.91)	**4.31 (0.04)**	0.04 (0.85)	0.42 (0.52)	0.01 (0.93)
TNF-α	0.26 (0.05)	2.86×10^{-08}	**70.40 (4.84×10^{-17})**	0.52 (0.47)	**9.39 (2.18×10^{-03})**	0.50 (0.48)	**5.65 (0.02)**	**27.93 (1.26×10^{-07})**
IL-6	0.17 (0.05)	5.46×10^{-05}	**30.24 (3.82×10^{-08})**	2.32 (0.13)	2.00 (0.16)	1.59 (0.21)	0.19 (0.66)	**123.55 (1.06×10^{-28})**
IL-8	0.30 (0.05)	4.54×10^{-14}	**87.94 (6.73×10^{-21})**	**4.56 (0.03)**	**19.07 (1.26×10^{-05})**	1.10 (0.29)	**5.80 (0.02)**	1.17 (0.28)

Table 3.

Bivariate polygenic analysis results each suicide trait (lifetime suicide attempt and current suicidal ideation) paired with an inflammatory marker (TNF-α, IL-6, IL-8). including ρ_g (and standard error) estimates and p-values.

Suicide Trait	Inflammation Marker	ρ_g(se)	p_{FDR}
Lifetime Suicide Attempt	TNF-α	0.10 (0.10)	0.60
	IL-6	0.37 (0.23)	0.12
	IL-8	**0.49 (0.17)**	**8.94x10^{-03}**
Current Suicidal Ideation	TNF-α	0.15 (0.20)	0.47
	IL-6	0.39 (0.23)	0.15
	IL-8	0.29 (0.16)	0.15