



Higher Levels of Interleukin-6 and Tumor Necrosis Factor- α are Associated with Suicidal Ideation in Adolescents

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INTRODUCTION

- Suicide is the second leading cause of death in the United States in youth 10-24 years of age.^{1,2}
- Major Depressive Disorder (MDD), which commonly has its first onset during adolescence,^{3,4} is a significant risk factor for suicidal ideation (SI).⁵
- Identifying biomarkers of SI may facilitate early detection of risk for suicide
- Pro-inflammatory cytokines (especially IL-6 and TNF- α) have been implicated in the pathophysiology of depression and SI in adults;^{6,7} we know less, however, about inflammatory markers and their association with SI in adolescents.⁸

STUDY AIM

Examine the association between current SI and peripheral inflammation in depressed adolescents and age- and sex-matched healthy controls.

METHODS

STUDY SAMPLE

- 38 depressed adolescents and 20 healthy controls were recruited from the San Francisco Bay Area.

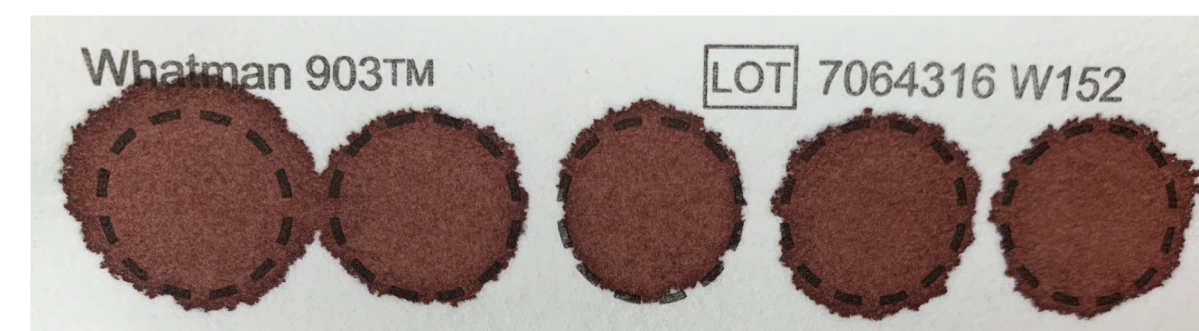
MEASURES

- **Diagnostic Status:** We administered the *Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-PL)*⁹ to determine MDD and CTL status.
 - MDDs met current threshold or subthreshold criteria for a DSM-IV depressive disorder (MDD, DDNOS, Dysthymia).
 - CTLs had neither personal nor family history of any current or past Axis I psychiatric disorder.
- **Depression Severity:** Current depression severity (past two weeks) was assessed with the *Reynolds Adolescent Depression Scale (RADS-2)*.¹⁰
- **Current Suicidal Ideation:** Frequency and severity of current (past month) SI was measured using the *Suicidal Ideation Questionnaire-Junior High Version (SIQ-JR)*.¹¹

Variable	MDD (N=38)	CTL (N=20)	Test Statistic	p-value
Age	16.45 ± 1.24	15.89 ± 1.06	$t(56) = 1.72$	0.090
Sex	Female: 29	Female: 12	$\chi^2(1) = 0.99$	0.320
BMI	23.15 ± 5.40	21.28 ± 2.89	$t(56) = 1.44$	0.155
RADS-2	63.71 ± 8.45	41.65 ± 6.94	$t(56) = 10.02$	4.29e-14
SIQ-JR	24.29 ± 17.94	2.55 ± 3.75	$t(56) = 7.18$	7.26e-09

DRIED BLOOD SPOT (DBS) PROTOCOL

- Blood spots were collected on 1.3 cm Whatman filter paper then dried overnight before being frozen at -20°C.
- DBS samples were extracted, centrifuged, and diluted 3-fold in a Luminex assay buffer prior to being run on a 62-plex immunopanel (eBiosciences, San Diego, CA) on the Luminex FlexMap 3D.
- Given evidence of higher sensitivity in fluorescence intensity values over concentration estimates in low abundance analytes from multiplex assays, we used median fluorescence intensity (MFI) values in all analyses.¹²
- Log transformed MFI values for IL-6 and TNF- α , corrected for non-specific binding using orthogonal non-linear least squares (*onls* package in R) were used in all statistical analyses.^{13,14}

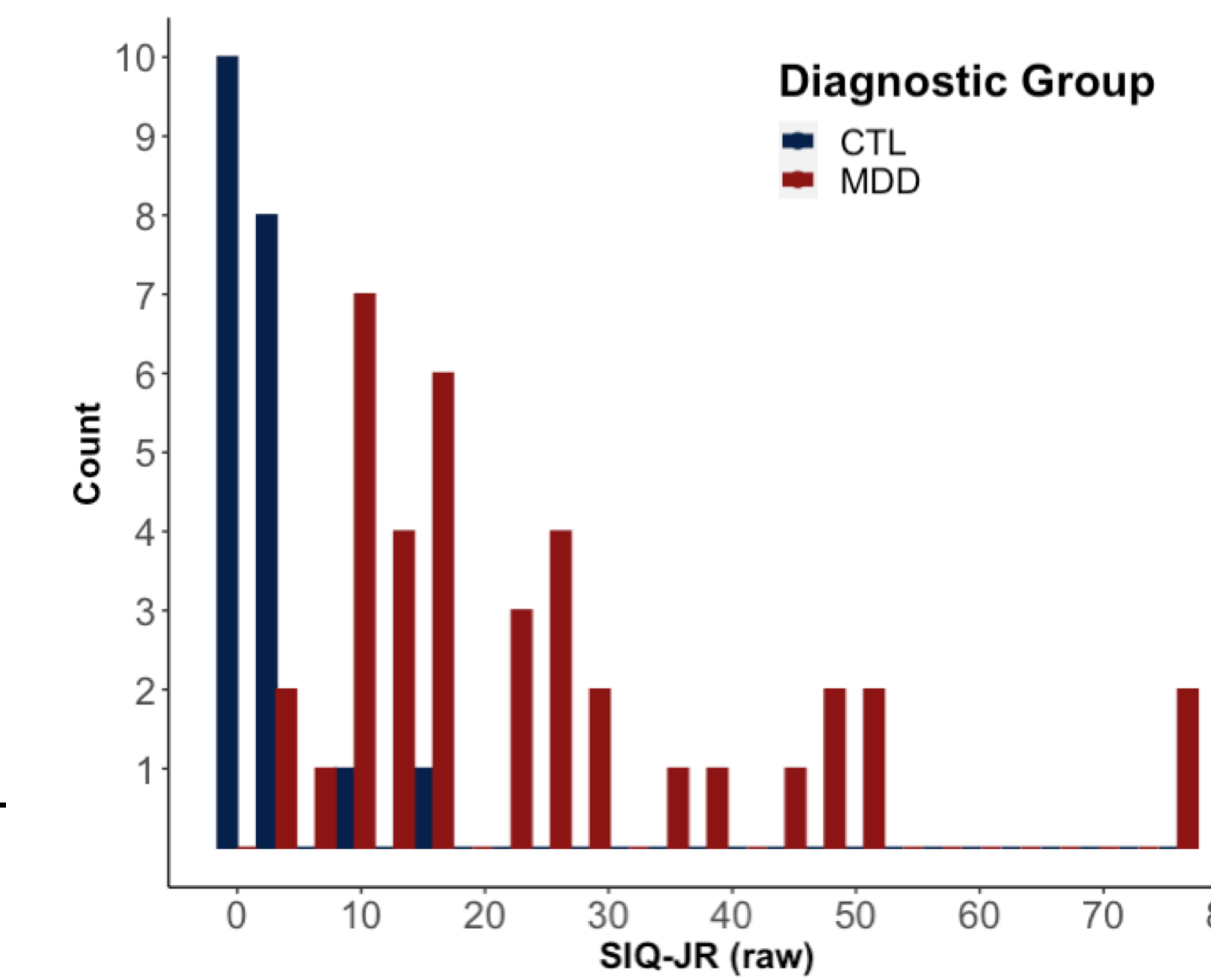


Example DBS sample

Variable	MDD (N=38)	CTL (N=20)	Test Statistic	p-value
IL-6 (log)	4.57 ± .13	4.50 ± .15	$t(56) = 1.74$	0.088
TNF- α (log)	4.83 ± .17	4.77 ± .16	$t(56) = 1.34$	0.184

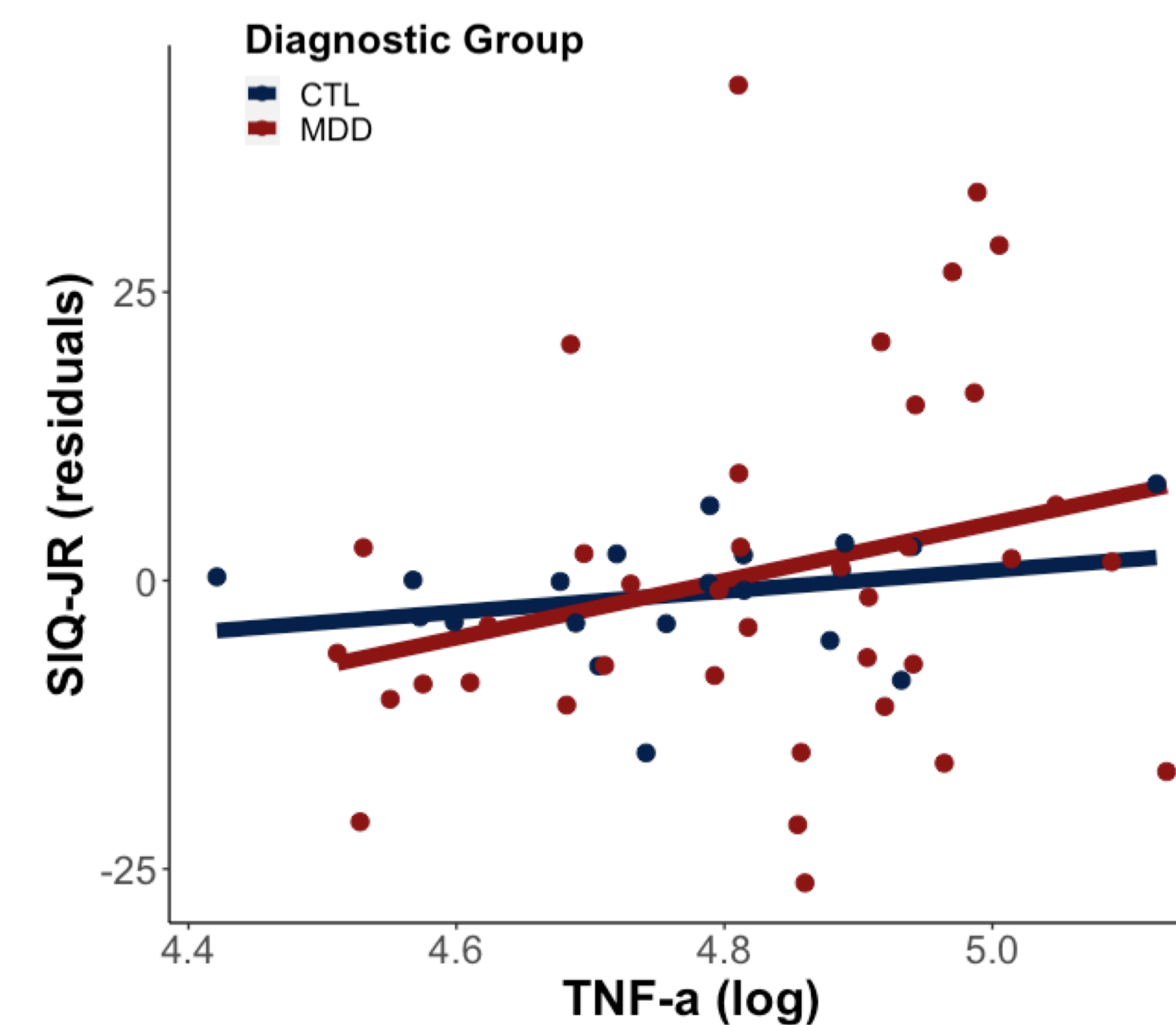
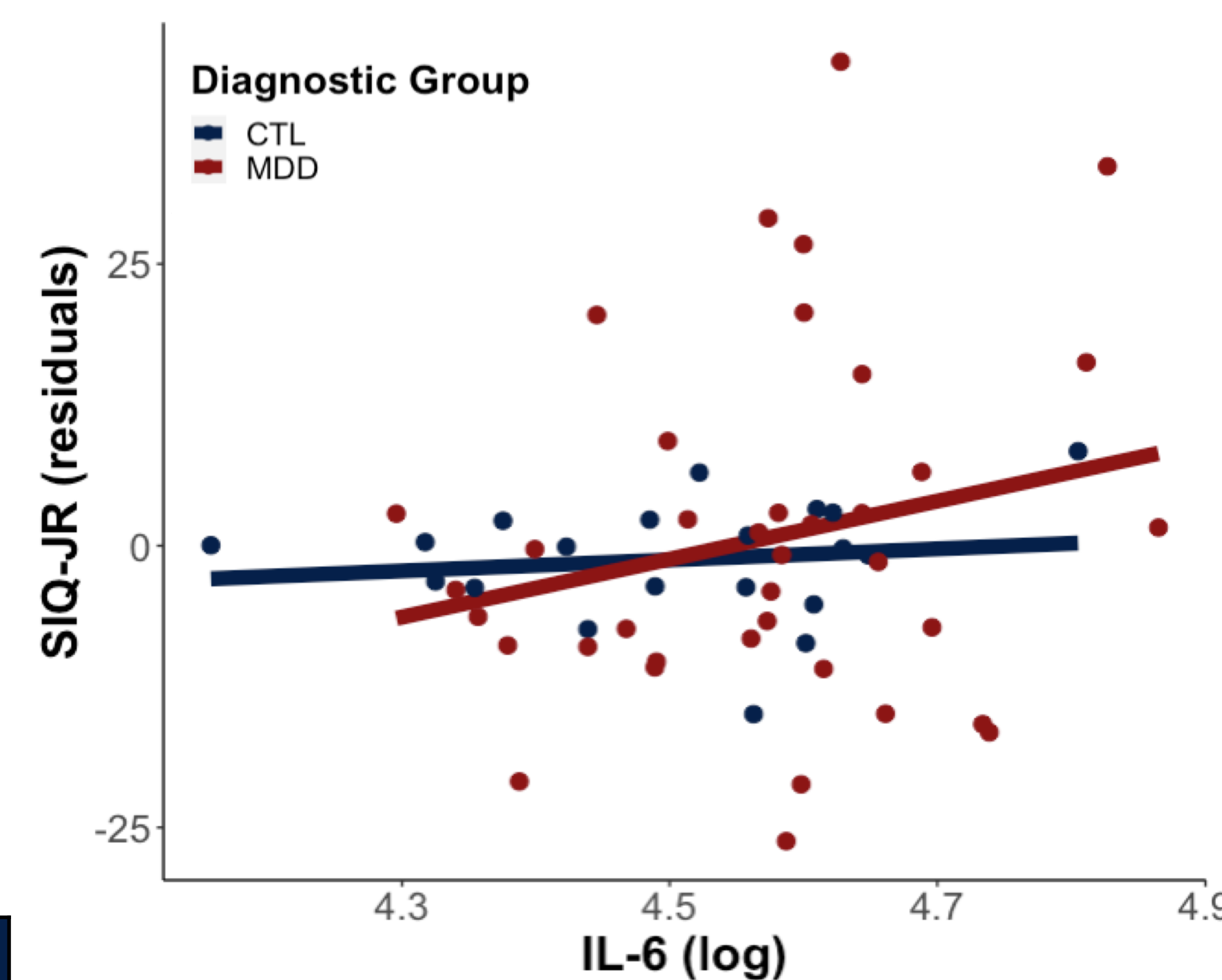
RESULTS

- Because of the skewed distribution of SIQ-JR raw scores, we conducted negative binomial regressions covarying for age, sex, BMI, RADS-2 *t*-scores, and allergy/corticosteroid medication use.
- For visualization purposes, we plotted the log-transformed pro-inflammatory cytokine values of interest on the x-axis with the residuals of SIQ-JR scores regressed on all covariates on the y-axis.



PRIMARY ANALYSES

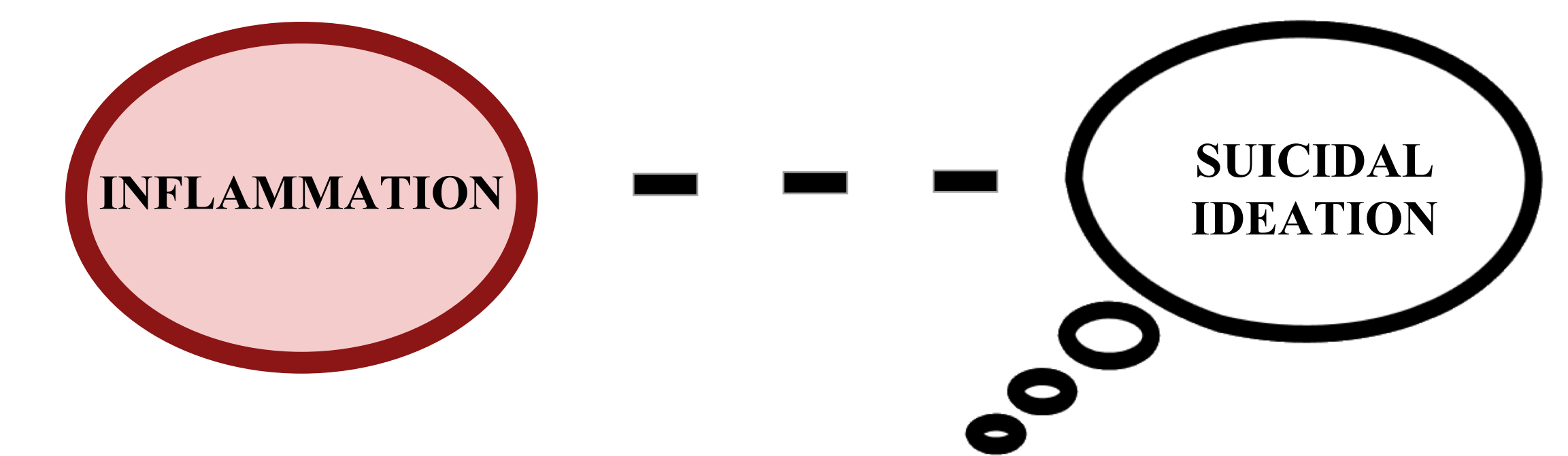
- In the full sample, both IL-6 and TNF- α were positively associated with SIQ-JR scores.
- In the MDD subsample, *only* TNF- α was associated with SIQ-JR scores.



- **Full sample:** $B=1.86 \pm 0.79$, $z(51) = 2.37$, $p=0.018$
- **MDD subsample:** $B=1.02 \pm 0.75$, $z(31) = 1.35$, $p=0.176$
- **Full sample:** $B=2.3 \pm 0.64$, $z(51) = 3.62$, $p<0.001$
- **MDD subsample:** $B=1.37 \pm 0.6$, $z(31) = 2.24$, $p=0.025$
- *Linear regressions revealed that neither IL-6 nor TNF- α were associated with depression severity, as measured by RADS-2 t-scores, either in the full sample or in the MDD subsample.*

CONCLUSIONS

Concentrations of IL-6 and TNF- α were positively associated with levels of SI reported in the past month in a sample of adolescents with and without depression. Furthermore, TNF- α was a robust predictor of SI within the sample of depressed adolescents, independent of severity of depression.



DISCUSSION

- Levels of pro-inflammatory cytokines may be a promising biomarker of suicidal ideation in adolescents.
- Given the scalability of DBS protocols, these findings could indicate an important risk factor for suicidality and may potentially be an important biological target for intervention.

LIMITATIONS & FUTURE DIRECTIONS

- Our sample size was relatively small; our results need to be replicated in larger samples.
- Longitudinal research is needed to further examine the potential mechanistic relations among pro-inflammatory cytokines, SI, and depression in adolescents.
- Suicidal ideation is a transdiagnostic phenomenon; future research should continue to examine the relationship between inflammation and SI in other disorders (e.g., PTSD, eating disorders) and in relation to suicidal and non-suicidal self injurious behaviors.

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