

Racial and Ethnic Disparities in the Incidence of Anti-NMDA Receptor Encephalitis

Samir Alsalek, BS, Kathryn B. Schwarzmann, BA, Sakar Budhathoki, BA, Viridiana Hernandez-Lopez, BA, Jessica B. Smith, Bonnie H. Li, and Annette Langer-Gould, MD, PhD

Correspondence

Dr. Langer-Gould
annette.m.langer-gould@kp.org

Neurol Neuroimmunol Neuroinflamm 2024;11:e200255. doi:10.1212/NXI.000000000200255

Abstract

Objectives

To estimate the incidence of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis.

Methods

We conducted a retrospective cohort study of >10 million person-years of observation from members of Kaiser Permanente Southern California, 2011–2022. The electronic health record of individuals with text-string mention of *NMDA* and *encephalitis* were reviewed to identify persons who met diagnostic criteria for anti-NMDAR encephalitis. Age-standardized and sex-standardized incidences stratified by race and ethnicity were estimated according to the 2020 US Census population.

Results

We identified 70 patients who met diagnostic criteria for anti-NMDAR encephalitis. The median age at onset was 23.7 years (IQR = 14.2–31.0 years), and 45 (64%) were female patients. The age-standardized and sex-standardized incidence of anti-NMDAR encephalitis per 1 million person-years was significantly higher in Black (2.94, 95% CI 1.27–4.61), Hispanic (2.17, 95% CI 1.51–2.83), and Asian/Pacific Island persons (2.02, 95% CI 0.77–3.28) compared with White persons (0.40, 95% CI 0.08–0.72). Ovarian teratomas were found in 58.3% of Black female individuals and 10%–28.6% in other groups.

Discussion

Anti-NMDA receptor encephalitis disproportionately affected Black, Hispanic, or Asian/Pacific Island persons. Ovarian teratomas were a particularly common trigger in Black female individuals. Future research should seek to identify environmental and biological risk factors that disproportionately affect minoritized individuals residing in the United States.

Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a rare subacute, rapidly progressive autoimmune encephalitis that can result in severe permanent neurologic deficits or death. Prior case-only, referral center–based studies^{1–3} describe a preponderance of anti-NMDAR encephalitis in female individuals, young adults, a strong association with ovarian teratomas, and rarely, with herpes simplex virus (HSV) encephalitis. The only multiethnic referral center–based cohort was composed of 32.1% White patients,² suggesting racial and ethnic disparities in anti-NMDAR encephalitis, but this was not investigated further.

From the Kaiser Permanente Bernard J. Tyson School of Medicine (S.A., K.B.S., S.B., V.H.-L.); Department of Research and Evaluation (J.B.S., B.H.L.); Department of Neurology (A.L.-G.), Los Angeles Medical Center, Southern California Permanente Medical Group; and Department of Clinical Science (A.L.-G.), Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA.

Go to [Neurology.org/NN](https://www.neurology.org/NN) for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

The crude incidence of anti-NMDAR encephalitis in the Netherlands is estimated at 1 per million.⁴ No prior studies have examined potential variation by race and ethnicity. The purpose of this study was to estimate the incidence of anti-NMDAR encephalitis in a large multiethnic, population-based cohort and determine whether it varies by race and ethnicity, sex, or age.

Methods

We conducted a retrospective cohort study using Kaiser Permanente Southern California's (KPSC) complete electronic health records (EHR), which include all inpatient and outpatient encounters, laboratory and imaging tests, diagnoses, medications, and demographic characteristics. KPSC provides comprehensive health care to >4.8 million members, representing approximately 20% of the general population in Southern California. The sociodemographic characteristics of KPSC members are representative of the underlying population.^{5,6}

Potentially incident cases were identified using a text-string search for *NMDA* and *encephalitis* mentioned in the same encounter between January 1, 2011, and December 31, 2022 (n = 803, eFigure 1). The EHR was abstracted to confirm patients met diagnostic criteria for definite (positive CSF antibodies, n = 67) or probable (n = 3, missing CSF results) anti-NMDAR encephalitis.^{1,7}

Race and ethnicity, surrogates for structural racism,⁸ were obtained from record review (cases only) and the EHR. We categorized race and ethnicity as White (non-Hispanic White), Hispanic (White, Hispanic), Black (regardless of ethnicity), Asian or Pacific Islander (PI), other or multiple races/ethnicities, and unknown because of missing information (0% of cases).

Standard Protocol Approvals, Registrations, and Patient Consents

The institutional review board at (KPSC) approved this study. Informed consent was waived because there was no direct patient contact.

Statistical Analyses

Incidence rates (IRs) were calculated by dividing the number of newly diagnosed cases in the group by the sum of person-years contributed by each member of that group. Confidence intervals (CIs) for IRs and incidence risk ratios (IRR) were calculated using Poisson regression. Age-adjusted and sex-adjusted (male, female) standardized incidence rates were calculated according to the 2020 US Census population. Annual variations in IRs were examined to minimize detection bias (2009–2022, eTable 1). The mean values and SDs of normally distributed variables were compared using 2-sample *t* tests; for binary or categorical variables, the χ^2 test with Fisher exact test was used. All analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC). Sensitivity analyses excluding probable cases were performed.

Data Availability

Due to the KPSC institutional review board, data will be available upon reasonable request.

Results

Demographic and Clinical Characteristics

The clinical and demographic characteristics of individuals newly diagnosed with anti-NMDAR encephalitis stratified by race and ethnicity are summarized in Table 1. The median age at diagnosis was 23.8 years (range 2.5–68.2 years), and 45 (64%) were female patients. The median time from symptom onset to clinical diagnosis was 17 days (IQR 9–26 days) and was significantly longer in male patients compared with female individuals (23 vs 14 days, $p = 0.006$) but did not differ significantly between racial/ethnic or age groups (eTable 2). CSF pleocytosis (70%) and abnormal EEG (73%) were common, but abnormal brain MRI (n = 28, 40%) less so.

Ovarian teratomas were found in 21 female patients (median age = 24.5 years, range 9.1–42.2) and a mediastinal teratoma in 1 Black male patient. Ovarian teratomas were significantly more common in Black female patients compared with other racial/ethnic groups, accounting for two-thirds of Black patients with anti-NMDAR encephalitis. HSV encephalitis preceded the onset of anti-NMDAR encephalitis in 3 patients by 1.3, 1.7, and 12.5 months. Most of the patients (n = 43, 61.4%) had no identifiable trigger, particularly those younger than 13 years (n = 12, 81.3%) compared with other age groups (n = 26, 59.1% ≤ 13–40 years; n = 4, 40.0% > 40 years, $p = 0.012$; eTable 2).

Incidence

The age-adjusted and sex-adjusted standardized incidence rates of anti-NMDAR encephalitis were higher in Black, Asian/PI, and Hispanic individuals than White persons (Figure). The risk of anti-NMDAR encephalitis was 7.01 (95% CI 2.63–18.70; $p < 0.0001$) higher in Black, 4.36 (95% CI 1.58–12.00; $p = 0.0044$) higher in Asian/PI, and 4.28 (95% CI 1.82–10.11, $p = 0.0009$) higher in Hispanic individuals compared with that in White persons (reference group). The age-standardized incidence rate was significantly higher among Black (IRR = 16.28, 95% CI 3.57–74.32, $p = 0.0003$), Asian/PI (IRR = 9.73, 95% CI 2.06–45.82, $p = 0.0040$), and Hispanic (IRR = 7.21, 95% CI 1.70–30.48, $p = 0.0073$) individuals compared with White female patients (reference group). Age-standardized incidence was similar between Black, Asian/PI, and White male patients but higher in Hispanic (IRR = 2.86, 95% CI 0.95–8.56, $p = 0.0609$) than White male patients (reference group), although this finding did not reach statistical significance. After considering the racial/ethnic distribution of the US population, we estimate that approximately 400 individuals will be newly diagnosed with anti-NMDAR encephalitis per year in the United States (Table 2). Analyses excluding probable cases yielded similar results (eTable 3).

Discussion

That Black, Asian, and Hispanic individuals have 7- to 4-fold higher incidence of anti-NMDAR encephalitis than White individuals is a novel finding. Presence of antibodies against the NMDAR in CSF is pathologic and establishes the

diagnosis in symptomatic patients.¹ Yet, reliable estimates of incidence exist are challenging to generate because the disease is very rare, relatively new, and case identification in large populations is challenging without a specific ICD code. The only existing reliable estimate reported a crude estimate of 1.00/million although with confidence limits (0.62–1.59) that

Table 1 Clinical and Demographic Characteristics of Persons With Incident Anti-NMDAR Encephalitis Race/Ethnicity

	White n = 6	Hispanic n = 42	Black n = 12	Asian/PI n = 10	Total n = 70	p Value
Age at diagnosis, y, median (IQR)	31.2 (24.8–37.6)	19.6 (11.6–28.1)	28.1 (23.8–42.1)	27.7 (11.7–29.5)	23.8 (14.3–31.0)	0.01
<13, n (%)	0 (0)	13 (31.0)	0 (0)	3 (30.0)	16 (22.9)	0.07
≥13–40, n (%)	5 (83.3)	24 (57.1)	8 (66.7)	7 (70.0)	44 (62.9)	
>40, n (%)	1 (16.7)	5 (11.9)	4 (33.3)	0 (0)	10 (14.3)	
Time from symptom onset to diagnosis, d, median (IQR)	30.5 (9.0–59.0)	17.5 (11.0–25.0)	15.5 (7.0–22.0)	12.0 (6.0–23.0)	17.0 (9.0–26.0)	0.43
Female, n (%)	2 (33.3)	25 (59.5)	10 (83.3)	8 (80.0)	45 (64.3)	0.13
Presenting symptoms, n (%)						
Seizures	3 (50.0)	22 (52.4)	7 (58.3)	4 (40.0)	36 (51.4)	0.89
Psychobehavioral symptoms	6 (100.0)	41 (97.6)	12 (100)	9 (90.0)	68 (97.1)	0.44
Movement disorders	3 (50.0)	16 (38.1)	8 (66.7)	9 (90.0)	36 (51.4)	0.01
Sleep disturbances	1 (16.7)	21 (50.0)	3 (25.0)	3 (30.0)	28 (40.0)	0.25
Clinical triggers, n (%)						
None	3 (50.0)	29 (69.0)	3 (25.0)	8 (80.0)	43 (61.4)	0.002
Teratoma/dermoid tumors	1 (16.7)	12 (28.6)	8 (66.7)	1 (10.0)	22 (31.4)	
HSV infection	2 (33.3)	1 (2.4)	0 (0)	0 (0)	3 (4.3)	
Other viral trigger^a	0 (0)	0 (0)	0 (0)	1 (10.0)	1 (1.4)	
Other tumor^b	0 (0)	0 (0)	1 (8.3)	0 (0)	1 (1.4)	
CSF/serum antibody tests, n (%)						
At least 1 positive	5 (83.3)	41 (97.6)	12 (100)	9 (90.0)	67 (95.7)	0.15
CSF not done/serum negative	1 (16.7)	1 (2.4)	0 (0.0)	1 (10.0)	3 (4.3)	
CSF pleocytosis present^c, n (%)	3 (50.0)	29 (69.0)	9 (75.0)	8 (80.0)	49 (70.0)	0.71
MRI, n (%)						
Normal	3 (50.0)	26 (61.9)	5 (41.7)	8 (80.0)	42 (60.0)	0.16
Abnormal, unilateral	0 (0)	4 (9.5)	2 (16.7)	2 (20.0)	8 (11.4)	
Abnormal, bilateral	3 (50.00%)	12 (28.6)	5 (41.7)	0 (0)	20 (28.6)	
EEG^d, n (%)						
Normal	4 (66.7)	9 (21.4)	2 (16.7)	1 (10.0)	16 (22.9)	0.03
Abnormal	1 (16.7)	31 (73.8)	10 (83.3)	9 (90.0)	51 (72.9)	

Abbreviations: HSV = herpes simplex virus; IQR = interquartile range; NMDAR = N-methyl-D-aspartate receptor; PI = Pacific Islander.

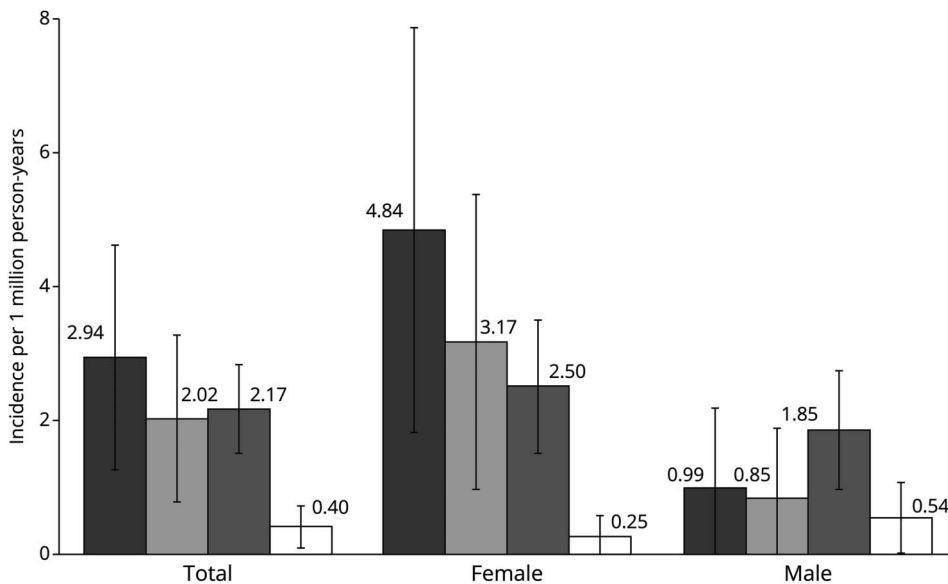
^a Patient had concomitant RSV infection at the same time of NMDAR onset.

^b Lung mass in smoker who died before biopsy could be obtained.

^c CSF testing was not performed in 1 White and 1 Black patient.

^d EEG was not performed/report not found for 1 White patient and 2 Hispanic patients.

Figure Incidence of Anti-NMDAR Encephalitis by Race/Ethnicity and Sex



This graph shows the annual incidence rates (indicated by the number above each bar) and 95% confidence intervals of anti-NMDAR encephalitis standardized by age and sex (total) or age alone (female, male) to the 2020 US Census in Black (in black), Asian/Pacific Islander (PI) (in gray), Hispanic (in dots), and White (in white) persons by sex. The overall increased incidence of NMDAR in Black, Asian/PI, and Hispanic individuals compared with White individuals is driven by a significantly higher incidence in Black (4.84, 95% CI 1.81–7.86), Asian/PI (3.17, 95% CI 0.97–5.37), and Hispanic (2.51, 95% CI 1.52–3.49) female individuals compared with White female individuals (0.25, 95% CI 0.00–0.60). The age-standardized incidence was highest in Hispanic male individuals (1.85, 95% CI 0.97–2.73) and lowest in White male individuals (0.94, 95% CI 0.01–1.06), but this difference did not reach statistical significance.

overlap with the rate in White people in our study. While another study attempted to estimate the incidence of autoimmune encephalitides in White individuals, it was limited by a small sample (~3.3 million person-years), a timeframe (1995–2015) largely before the first description of anti-NMDAR encephalitis (2007), and identified only 1 patient with anti-NMDAR encephalitis.⁹

Consistent with prior studies, we found an association with ovarian teratomas² highest in Black patients¹⁰ and rarely in young female patients²; rare association with HSV encephalitis; and high frequency of neuropsychiatric features, CSF pleocytosis, abnormal EEGs, and normal brain MRIs² at anti-NMDAR encephalitis presentation. We found a lower female preponderance in Hispanic individuals compared with Black

and Asian individuals in this study and compared with prior studies in non-Hispanic populations.^{2,4}

This study is limited by a relatively small number of cases, particularly among White individuals and in the youngest and oldest age groups, variation in timing and type of EEGs and MRIs, lack of socioeconomic status data, and the inherent challenges in lumping large groups of people with diverse cultures and ancestral backgrounds into limited racial and ethnic categories. Whether findings from California can be extrapolated to other diverse populations is also unknown and should be addressed in future studies. Strengths include an exhaustive search strategy to identify cases, long study period improving precision, and decreasing the possibility of underdetection.

Table 2 Standardized Incidence Rates and Estimated Number of Newly Diagnosed Individuals With Anti-NMDAR Encephalitis Annually in the United States by Race/Ethnicity

Race/ethnicity	Cases with anti-NMDAR encephalitis	Active KPSC member person-years	Crude incidence per 1,000,000 person-years (95% CI)	Standardized incidence per 1,000,000 person-years (95% CI) ^a	US population in 2020 ^b	Expected newly diagnosed patients with anti-NMDAR encephalitis annually
White	6	15,838,182	0.38 (0.08–0.68)	0.40 (0.08–0.72)	191,722,195	77
Hispanic	42	20,126,744	2.09 (1.46–2.72)	2.17 (1.51–2.83)	65,329,087	142
Black	12	4,074,294	2.95 (1.28–4.61)	2.94 (1.27–4.61)	39,944,624	117
Asian/Pacific Islander	10	5,390,568	1.86 (0.71–3.01)	2.02 (0.77–3.28)	20,243,574	41
Total^c	70	45,429,789	1.54 (1.18–1.90)	—	317,239,480	377

Abbreviations: KPSC = Kaiser Permanente Southern California; NMDAR = N-methyl-D-aspartate receptor.

^a Standardized to the 2020 US Census and adjusted for age and sex.

^b Per 2020 US Census.

^c Includes persons with other/missing/unknown race and ethnicity.

Our study raises interesting questions about why minoritized individuals, particularly female individuals, in the United States may be more prone to aberrant humoral (and cell-mediated) immune responses. Current evidence suggests at best a weak association with certain human leukocyte antigen subtypes underscoring the importance of environmental factors in the development of anti-NMDAR encephalitis. Informed by the evidence in another autoimmune disease with a similar racial/ethnic distribution,¹¹ we speculate that racial/ethnic disparity in anti-NMDAR encephalitis in the United States may at least partly be attributable to the embodiment of socioeconomic and environmental factors including poverty, racial discrimination, substandard health care,^{8,12} and earlier exposure and more vigorous responses to common childhood infections.^{13,14} These factors and their potential influence on immunologic dysregulation and epigenetic changes that could predispose individuals to anti-NMDAR encephalitis should be examined in future studies.

Study Funding

The authors report no targeted funding.

Disclosure

A. Langer-Gould has received grant support and awards from the Patient-Centered Outcomes Research Institute, the National MS Society, and Atara Biotherapeutics. She currently serves as a voting member on the California Technology Assessment Forum, a core program of the Institute for Clinical and Economic Review (ICER). S. Alsalek, K.B. Schwarzmann, S. Budhathoki, V. Hernandez-Lopez, J.B. Smith, and B.H. Li report no disclosures relevant to the manuscript. Go to [Neurology.org/NN](https://www.neurology.org/NN) for full disclosures.

Publication History

Received by *Neurology: Neuroimmunology & Neuroinflammation* November 30, 2023. Accepted in final form March 14, 2024. Submitted and externally peer reviewed. The handling editor was Editor Josep O. Dalmau, MD, PhD, FAAN.

Appendix Authors

Name	Location	Contribution
Samir Alsalek, BS	Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Kathryn B. Schwarzmann, BA	Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Sakar Budhathoki, BA	Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data

Appendix (continued)

Name	Location	Contribution
Viridiana Hernandez-Lopez, BA	Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Jessica B. Smith	Department of Research and Evaluation, Southern California Permanente Medical Group, Pasadena, CA	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Bonnie H. Li	Department of Research & Evaluation, Southern California Permanente Medical Group, Pasadena, CA	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Annette Langer-Gould, MD, PhD	Department of Neurology, Los Angeles Medical Center, Southern California Permanente Medical Group; Department of Clinical Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

References

- Dalmau J, Armangué T, Planagumà J, et al. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. *Lancet Neurol*. 2019;18(11):1045-1057. doi:10.1016/S1474-4422(19)30244-3
- Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol*. 2013;12(2):157-165. doi:10.1016/S1474-4422(12)70310-1
- Thaler FS, Zimmermann L, Kammermeier S, et al. Rituximab treatment and long-term outcome of patients with autoimmune encephalitis: real-world evidence from the GENERATE registry. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(6):e1088. doi:10.1212/NXI.0000000000001088
- Bastiaansen AEM, de Bruijn MAAM, Schuller SL, et al. Anti-NMDAR encephalitis in The Netherlands, focusing on late-onset patients and antibody test accuracy. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(2):e1127. doi:10.1212/NXI.0000000000001127
- Koebnick C, Langer-Gould AM, Gould MK, et al. Sociodemographic characteristics of members of a large, integrated health care system: comparison with US Census Bureau data. *Perm J*. 2012;16(3):37-41. doi:10.7812/TPP/12-031
- Davis AC, Voelkel JL, Remmers CL, Adams JL, McGlynn EA. Comparing kaiser permanente members to the general population: implications for generalizability of research. *Perm J*. 2023;27(2):87-98. doi:10.7812/TPP/22.172
- Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol*. 2016;15(4):391-404. doi:10.1016/S1474-4422(15)00401-9
- Krieger N. Methods for the scientific study of discrimination and health: an ecosocial approach. *Am J Public Health*. 2012;102(5):936-944. doi:10.2105/AJPH.2011.300544
- Dubey D, Pittock SJ, Kelly CR, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. *Ann Neurol*. 2018;83(1):166-177. doi:10.1002/ana.25131
- Shahrestani S, Brown NJ, Singh R, et al. Evaluating the incidence and predictors of anti-NMDAR encephalitis in a contemporary cohort of patients diagnosed with dermoid tumors: a national inpatient sample analysis. *J Clin Neurosci*. 2022;102:109-113. doi:10.1016/j.jocn.2022.06.018
- Lewis MJ, Jawad AS. The effect of ethnicity and genetic ancestry on the epidemiology, clinical features and outcome of systemic lupus erythematosus. *Rheumatology (Oxford)*. 2017;56(suppl_1):i67-i77. doi:10.1093/rheumatology/kew399
- Williams DR, Sternthal M. Understanding racial-ethnic disparities in health: sociological contributions. *J Health Soc Behav*. 2010;51(Suppl):S15-S27. doi:10.1177/0022146510383838
- Ford JL, Stowe RP. Racial-ethnic differences in Epstein-Barr virus antibody titers among U.S. children and adolescents. *Ann Epidemiol*. 2013;23(5):275-280. doi:10.1016/j.annepidem.2013.02.008
- Dowd JB, Palermo T, Chyu L, Adam E, McDade TW. Race/ethnic and socioeconomic differences in stress and immune function in the National Longitudinal Study of Adolescent Health. *Soc Sci Med*. 2014;115:49-55. doi:10.1016/j.socscimed.2014.06.011