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Community violence and cellular and cytokine indicators of inflammation in adolescents

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ABSTRACT

Neighborhood violence is associated with a range of health consequences but little is known about the biological processes involved. Research in disease pathogenesis has identified low-grade inflammation as a process that, beginning in the first decades of life, is both induced by chronic stress and a contributor to multiple cardiometabolic diseases that present throughout the lifecourse. Previous research has examined whether neighborhood violence is associated with inflammatory biomarkers, but has been limited to cytokine indicators of inflammation. In a sample of adolescents (n = 203) residing in Chicago, we tested cross-sectional associations between neighborhood violence and cellular and cytokine indicators of inflammation. Neighborhood-level violence was measured in multiple ways (as murder rates of Census block groups and as the sum of homicides within 1 and ½ mile zones) in the areas surrounding where youth lived and attended school. At the individual level, violence exposure was measured by self-report (direct victimization, witnessing violence, and/or victimization of family or friends in the past year). Adolescents residing in high-violence neighborhoods evidenced higher numbers of pro-inflammatory classical (CD14+ +CD16-) monocytes relative to those in less violent neighborhoods. In contrast, neighborhood-level violence was not consistently associated with cytokine levels across different model specifications. Self-reported violence exposure was also not consistently associated with inflammatory biomarkers. Neighborhood-level violence and self-reported violence exposure interacted, such that the positive association between neighborhood-level violence and classical monocytes was observed only among adolescents who reported being exposed to violence. Associations were largely specific to the neighborhoods in which youth lived as opposed to those in which they attended school. Findings provide the first evidence that youth residing in high-violence neighborhoods show mobilization of classical monocytes, suggesting a pro-inflammatory mechanism through which contextual stressors such as neighborhood violence may compromise health.

Gun violence remains a major public health concern in the United States, especially in large metropolitan areas of the country where it disproportionately occurs (Pew Research Center, 2018). Young people residing in high-violence neighborhoods are especially vulnerable, not only because of the threat that community violence poses to their safety, but also because community violence can have significant and widespread consequences for development—including increasing behavioral and academic difficulties, decreasing cognitive and self-regulatory capacities, and increasing the risk of developing psychopathology, post-traumatic stress symptoms and adjustment problems (Margolin and Gordis, 2004; Foster and Brooks-Gunn, 2009; Sharkey, 2018). Less well-understood are costs to physical health, although new research suggests that community violence is associated with poorer cardiovascular functioning in youth (Wright et al., 2017) and adults (Ford and Browning, 2014; Mayne et al., 2018). Little is known, however, about the biological processes involved.

Community violence can have extensive effects that not only affect individuals who are directly victimized, but also and importantly, individuals in the community who are not direct victims (Sharkey, 2018). For example, instances of extreme violence including homicides negatively impact the psychological functioning of youth who live near such crimes, but who are neither direct victims nor witnesses themselves—suggesting that local violence can have indirect or "vicarious" effects on youth (Sharkey, 2010; Sharkey et al., 2012). Community

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violence reduces one's sense of safety and increases feelings of distress (Foster and Brooks-Gunn, 2009). Hearing about community violence causes individuals and families to engage in coping strategies to increase personal safety (e.g., limiting outdoor time, constraining daily life to avoid specific settings; Rosenblatt and DeLuca, 2012). Thus, in addition to questions about biological mechanisms, the question of *who* is vulnerable to the health consequences of community violence is not well understood (e.g., is it those who are victimized themselves or, alternatively/additionally, those who live in close proximity to violent crime but who are not necessarily victimized).

One plausible mechanism that might explain the association between community violence and health is persistent low-grade inflammation, which can result from stress-related changes in health practices and/or neuro-hormonal activity (Miller et al., 2011). There is now strong evidence that low-grade inflammation is involved in the pathogenesis of multiple health problems across the lifespan, and in particular manifestations of cardiometabolic disease including obesity, diabetes, metabolic syndrome, atherosclerosis, and stroke (Hotamisligil, 2006; Lackey and Olefsky, 2016; Libby et al., 2018). Consistent with this, childhood adversity is positively associated with circulating biomarkers of low-grade inflammation such as C-reactive protein (CRP) and interleukin-6 (IL-6) later in life (Danese et al., 2007; Slopen et al., 2013). Fewer studies have examined community violence specifically, although two recent studies are notable. For example, Broyles et al. (2012) observed that youth (ages 5–18) residing in high-crime or high-poverty neighborhoods were more likely to evidence elevated circulating levels of CRP than those in lower-crime or lower-poverty neighborhoods. Browning et al. (2012) observed in a large sample of adults (ages 30–65) that short-term neighborhood crime "spikes" (increases in burglary over one year) predicted higher levels of CRP in men by not women. While valuable as predictive tools, inflammatory biomarkers like IL-6 and tumor necrosis factor-α are released by multiple tissues (including adipose, bone, muscle, endothelial, and airway cells), and accordingly some unknown proportion of these biomarkers in circulation is non-immunologic. Moreover, in some of these tissues, cytokine actions are non-immunologic (Rocha and Libby, 2008). These observations raise questions about how cytokines in circulation should be interpreted with regard to inflammation and pathogenesis. Since CRP release is triggered by IL-6, the same interpretive issues apply to it. For a more direct measure of immune-related activity, one can examine the cells that initiate and maintain inflammation. Monocytes, immature blood-borne cells that differentiate into tissue macrophages and dendritic cells, are of particular interest in this regard (Miller et al., 2011). Monocytes can be differentiated into at least two subtypes: an immature, pro-inflammatory "classical" type (CD14 + + CD16- in humans) and a mature patrolling "non-classical" type (CD14 + CD16 + + in humans; Gordon and Taylor, 2005). Rodent models indicate that chronic social defeat preferentially mobilizes classical monocytes into circulation, via sympathetic innervation of the bone marrow (Wohleb et al., 2013; Weber et al., 2017).

Classical monocytes also seem to be selectively mobilized and activated in human adults facing chronic stressors, including low socioeconomic status and caregiving for a terminally ill family member (Miller et al., 2008, 2014b; Powell et al., 2013). Little is known about whether similar mobilization occurs in youth, or whether a broader contextual stressor like community violence can elicit it. We consider those issues here, asking whether youth residing in high-violence neighborhoods show mobilization of classical monocytes and higher levels of traditional inflammatory biomarkers. We expand the literature's focus on residential violence to also include areas surrounding children's schools given that travel to school is the primary reason why youth regularly leave their immediate residential neighborhoods (Loebach and Gilliland, 2016), and given evidence suggesting that violence in areas surrounding homes and schools may negatively influence psychological functioning in youth (DaViera and Roy, 2019). We had three main sets of hypotheses.

First, we predicted that youth residing and/or attending school within violent neighborhoods would evidence a pro-inflammatory phenotype, characterized by higher levels of inflammatory biomarkers (CRP and several circulating cytokines) and higher numbers of classical monocytes in circulation. We did not expect neighborhood violence to be associated with numbers of non-classical monocytes, given that these cells are less responsive to psychosocial stress and less inflammatory in nature than the classical type (Robbins and Swirski, 2010).

Second, we predicted that neighborhood-level violence and the inflammatory phenotype would be associated even when youths' self-report of previous exposure to violence (ETV; which includes direct victimization, victimization of family or friends, and witnessing violence) was considered. Such a pattern would be generally consistent with literature on cognitive outcomes, which shows that proximity to homicides has indirect or "vicarious" effects on nearby youth even when they were not victims and/or witnesses themselves (Sharkey, 2010; Sharkey et al., 2012).

Third, we explored interactive effects, predicting that the inflammatory phenotype would be most prominent among youth who both experienced ETV and resided in or attended school in high-violence neighborhoods. As explained above, there are reasons to expect that we might observe a positive association between neighborhood-level violence and inflammation even among youth who have not been victimized (consistent with the idea of indirect or vicarious effects). However, it is possible that this association would be even stronger for youth who have been personally exposed to violence, given, for example, that some of the consequences of personal violence exposure (e.g. increased stress- and trauma-related symptomatology and behavioral difficulties; Margolin and Gordis, 2004; Foster and Brooks-Gunn, 2009) may increase the perception of threat associated with neighborhood-level incidents and exacerbate associations with pro-inflammatory processes.

1. Method

1.1. Participants

277 adolescents (mean age = 13.9 years, SD = 0.5; min = 11.8, max = 15.3) from the greater Chicago area took part in a larger study on social disparities in cardiovascular risk. A purposive sampling strategy was used to recruit this sample so that it was similar demographically to youth and families in Cook County (in terms of race/ethnicity and the distribution of household income). Participants were recruited from advertisements in schools, on public transit, and local media outlets. To participate, youth had to be in good health and they were not eligible if they reported having an infectious disease in the past two weeks, were currently pregnant, or had a history of chronic medical or psychiatric illness. They also had to be free of prescription medications in the past month and without contraindications to MRI. Given our interest in testing multiple measures of neighborhood violent crime, and in particular, one method making use of publicly available geospatial data on homicides in the city of Chicago (see Measures section), the current analysis sample included only those youth living within the city limits of Chicago (n = 203). Of these 203 individuals, four attended school outside of Chicago. We were also unable to derive school data for one individual. School neighborhood analyses are thus conducted with an analytic sample of n = 198. Based on federal poverty thresholds established by the U.S. Census (www.census.gov), 21.2 % of youth in the analysis sample were from poor homes (income-to-needs ratio, INR < 1.0), 26.6 % from low-income homes (INR < 2.0), and 51.7 % from middle- (INR 2–4) and high- income homes (INR > 4). The analysis sample was similar to the population of families in the city of Chicago in terms of the percent of families designated as poor in 2015 (18.9 % of Chicago families), although the median household income of families in the sample ($46,500) was lower than that of Chicago families as a whole in 2015 ($50,702; www.

Table 1
Descriptives of the sample and analysis variables.

Individual and family characteristics	Mean (SD) or N (%)	
Inflammation composite	−0.004	(0.637)
Classical monocytes, count/μL	134.6	(55.3)
Non-classical monocytes, count/μL	33.8	(17.4)
Age, years	13.9	(0.5)
Sex, female	134	(66.0 %)
Race, Black	84	(41.4 %)
Race, White	60	(29.6 %)
Race, other	20	(9.8 %)
Ethnicity, Hispanic (any race)	77	(37.9 %)
Pre-, early-, or mid-puberty	59	(29 %)
Late or post-puberty	144	(71 %)
Family SES		
HH income-to-needs ratio	3.1	(4.4)
HH savings, thousands of dollars	96.0	(444.5)
Parent education, HS diploma or less	77	(37.9 %)
Exposure to violence (ETV)	2.1	(3.0)
No violence exposure	92	(45.3 %)
Home neighborhood exposures	Mean (SD)	
Murder rate, block-group	304.4	(265.2)
Community SES, block-group		
Median HH income, thousands of dollars	46.8	(24.8)
% pop. > 25 years without HS diploma	19.3	(13.3)
Sum of homicides within 1-mile	26.1	(21.3)
Sum of homicides within 1/2-mile	7.7	(7.4)
School neighborhood exposures	Mean (SD)	
Murder rate, block-group	267.2	(319.3)
Community SES, block-group		
Median HH income, thousands of dollars	50.9	(28.7)
% pop. > 25 years without HS diploma	17.5	(13.9)
Sum of homicides within 1-mile	29.5	(27.2)
Sum of homicides within 1/2-mile	7.6	(7.5)

Note: SES = socioeconomic status; HH = household; HS = high school.

chicagohealthatlas.org). The sample was racially/ethnically diverse (Table 1; 41.4 % of youth self-identified as Black or African American, 29.6 % White, 37.9 % Hispanic, 9.8 % other) and also similar in this regard to the target population in Chicago.

1.2. Procedure

Laboratory visits were conducted from years 2015–2017. At a laboratory visit, youth provided a fasting morning blood sample by antecubital venipuncture performed by trained phlebotomists. Parents and youth then completed a series of surveys and semi-structured interviews with a trained experimenter from which demographic and psychosocial data were collected. Laboratory visits lasted approximately 3.5 h. The study was approved by the Institutional Review Board of Northwestern University. A parent or legal guardian provided written consent for their and their child's participation and all youth gave written assent to participate.

1.3. Measures

1.3.1. Neighborhood-level violence

Participants' home and school addresses were geocoded using ArcGIS Pro Version 2.3 (ESRI, 2018) and linked to FIPS codes designating U.S. Census block groups. Block groups are geographic units established by the Census that represent between 600 and 3,000 individuals. Individual block groups were then linked to five-year (2011–2015) neighborhood murder rates, which are model-based estimates of the relative risk of homicide occurrence. These are based on crime reports that local law enforcement provide to the FBI's Uniform Crime Report and based on sociodemographic characteristics of block groups (Applied Geographic Solutions, Release 2017). The murder rate is scaled so that a value of 100 represents the national average. In the primary statistical models, values were divided by 100 so that a difference in one unit represented a difference of 100 on the original murder rate scale (e.g., from 100 to 200).

In supplementary analyses, neighborhood-level violence was operationalized by summing the number of homicides that took place within 1 mile and also ½ mile of participants' homes and schools. Data on the approximate spatial locations of homicides in Chicago from years 2011–2015 were downloaded from publicly-available crime datasets at the City of Chicago's Online Data Portal (https://data.cityofchicago.org). ArcGIS Pro was used to establish radial buffer zones (1-mile and ½-mile radiuses by Euclidean distance) around participants' geocoded home and school locations and the number of homicides within each buffer was summed.

1.3.2. Exposure to community violence

Recent exposure to violence (ETV) was measured using 7 self-report items capturing youth's exposure to various forms of violence (Thomson et al., 2002). Two items concerned whether youth had family or friends who had been victimized by violence (e.g., "Have any of your friends been hurt or killed by a violent act?"), two items concerned witnessing violence (e.g., "Have you ever seen or been present when someone was shot?"), and three items concerned direct victimization (e.g., "Have you ever been attacked with a knife or other sharp object?"). For each of the 7 items, youth reported whether the event had ever occurred, and if it had, how often it had occurred in the previous year. A frequency score was generated by summing the number of occurrences of any violence that youth experienced in the previous year. Because the distribution of responses was skewed in the positive direction, frequency scores above 10 (n = 11) were winsorized at the value of 10 (value at the 95th percentile).

1.3.3. Inflammatory biomarker composite

From fasting antecubital blood, we quantified serum levels of CRP, interleukin-6, interleukin-8, interleukin-10 and tumor necrosis factor-α (TNF-α). CRP was measured by high-sensitivity immunoturbidimetric assay on a Roche/Hitachi cobas c502 analyzer (lower limit of detection, 0.2 mg/L). The average intra- and inter-assay coefficients of variation were 2.5 % and 5.6 %. The cytokines were measured in duplicate by electrochemiluminescence on a SECTOR Imager 2400A (MesoScale Discovery) with a Human Pro-Inflammatory Ultra-Sensitive assay (MesoScale Discovery), following the manufacturer's instructions. The kit's lower limits of detection range from 0.19 pg/mL (IL-6) to 0.57 pg/mL (IL-10). Across runs, the intra-assay coefficients of variation for duplicate pairs were 4.01 % (IL-6), 4.59 % (IL-10), 3.00 % (IL-8), and 3.80 % (TNF-α). Raw values of each marker were log-10 transformed to correct for skew, and an inflammation composite was computed by standardizing these log-transformed scores and averaging them, following previous research (Miller et al., 2014a). A higher score on this composite reflects more low-grade inflammation. One case was missing inflammation composite data and was not included in analyses predicting the inflammation composite.

1.3.4. Classical and non-classical monocytes

A standardized flow cytometry protocol was used to enumerate populations of classical and non-classical monocytes (Heimbeck et al., 2010). Briefly, antecubital blood was drawn into Sodium-Heparin Vacutainers (Becton-Dickinson). After red blood cells had been removed (Pharm Lyse, Becton-Dickinson), the pelleted cells were washed, blocked with normal human serum, and stained with mouse, anti-human monoclonal antibodies against CD14 (FITC), CD16 (PE), HLA-DR (PerCPCy5.5), and CD45 (APC), all purchased from Becton-Dickinson. Following a 20-minute incubation, the cells were washed and fixed (CytoFix/ CytoPerm, Becton-Dickinson), and incubated for another 20 min. Data were acquired on a Guava 6HT2L (Millipore), with

30,000 events collected per specimen, and analyzed using FlowJo software (Tree Star Inc). Monocytes are identified by cell surface markers CD14 and CD16, which are differentially expressed in classical vs. non-classical cells (for review see Gordon and Taylor, 2005). Whereas classical monocytes express high numbers of CD14 and do not express CD16, non-classical monocytes express lower numbers of CD14 and higher numbers of CD16 (Gordon and Taylor, 2005). Following previous work (Heimbeck et al., 2010), populations of classical (CD14++/CD16-) and non-classical (CD14+/CD16++) monocytes were defined by a sequential gating procedure. Two cases were missing monocyte data and were not included in analyses predicting monocyte populations.

1.3.5. Covariates

Seven sociodemographic covariates were included in all statistical models and were determined a priori. These included child age (years, continuous), sex (0 = male; 1 = female), race (1 = White; 0 = non-White), and ethnicity (1 = Hispanic; 0 = non-Hispanic). Pubertal status was assessed using the Pubertal Development Scale, a validated five-item measure in which higher scores indicated more advanced puberty (Petersen et al., 1988). A family socioeconomic status (SES) composite was generated by standardizing (z-scoring) and averaging three commonly used indicators of economic need and social status: the income-to-needs ratio (INR; natural log transformed), financial savings, and parent education (ordinal scale corresponding to highest degree obtained by parent who attended lab visit). Lastly, in order to control for socioeconomic characteristics of participants' home and school neighborhoods, home and school neighborhood SES composites were generated by standardizing and averaging two block-group-level 5-year (2011–2015) estimates derived from the American Community Survey: median household income and the percent of adults in block group without a high school diploma (reverse-scored).

1.4. Statistical analyses

We first conducted a series of preliminary analyses that included descriptive statistics (Table 1) and zero-order correlations (Table 2) to explore study variables at univariate and bivariate levels, respectively. In order to address our primary research aims, the prediction of inflammatory biomarkers and monocyte subtypes by neighborhood violence, we conducted a series of generalized estimating equations (GEEs) in SPSS version 25. GEEs are an optimal analytic approach for the current research questions because they allow one to model the unique effects of the independent variables on the dependent variables, while statistically accounting for the correlated structure of the data (youth nested within block-groups). Statistical models were executed separately for each biomarker (i.e. the inflammation composite, classical monocytes, and non-classical monocytes) and for each neighborhood type (i.e., home and school neighborhoods). Thus, six models were conducted in total. In each model, the neighborhood murder rate (aggregated at the U.S. Census block group), self-reported violence exposure, and sociodemographic covariates (mean-centered) were entered simultaneously as independent variables (results from the six main effects models presented in Table 3). We then re-ran each model with the addition of an interaction term between the neighborhood murder rate and self-reported violence exposure. Simple slope analyses were used to interrogate any significant interactions that were observed. Graphical figures were generated using STATA version 16 and Microsoft Excel.

Supplementary analyses were undertaken to explore the sensitivity of the primary models to different specifications of neighborhood boundaries and violence. Specifically, main effects models (Table 4) were re-estimated with neighborhood violence first computed as the number of homicides within a one-mile radius of participants' homes or schools, and second, as the number of homicides within a 1/2-mile radius. Models in which the neighborhood murder rate and ETV were found to statistically interact were also re-estimated in these ways in order to estimate the sensitivity of the interaction effects.

2. Results

2.1. Descriptive analyses

2.1.1. Univariate statistics

Descriptive statistics of the sample and neighborhoods are presented in Table 1. On average, the murder rates of home (M = 304.4, SD = 265.2) and school (M = 267.2, SD = 319.3) neighborhoods were over 3 and 2.5 times the national average of 100.0, respectively. On average, youth lived within one mile of approximately 26 homicides from years 2011 to 2015, although there was wide variation (SD = 21.3 homicides; minimum = 0, maximum = 103). Within one half mile of participants' homes, there were fewer homicides, on average (M = 7.7, SD = 7.4). Youth reported on how often in the past year they had been personally exposed to violence in their communities. On average, youth reported exposure to 2.1 violent events in the past year (SD = 3.0), although 45.3 % of the sample reported no ETV in the previous year.

2.1.2. Zero-order correlations

Zero-order correlations among the analysis variables are shown in Table 2. There were small to moderate correlations at the bivariate level between the inflammatory biomarker composite, classical, and non-classical monocytes (rs ranged from .15 to .44) indicating that these are related but not redundant indicators of pro-inflammatory activity. There was a non-significant correlation between the inflammation

Table 2
Zero-order correlations of analysis variables.

		1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	Inflammation composite	1.00													
2	Classical monocytes	.28**	1.00												
3	Non-classical monocytes	.15*	.44**	1.00											
4	Home block group murder	.05	.17*	.02	1.00										
5	Home block group SES	−.08	−.01	−.03	−.41**	1.00									
6	School block group murder	−.01	.02	.02	.64**	−.29**	1.00								
7	School block group SES	−.04	.03	.00	−.23**	.33**	−.44**	1.00							
8	Exposure to violence	−.07	.01	−.05	.31**	−.23**	.27**	−.17*	1.00						
9	Child age	−.01	−.01	−.03	.08	−.21**	.04	−.05	.05	1.00					
10	Female	−.20**	−.07	.00	.00	.03	.00	.00	−.01	.06	1.00				
11	White	.06	−.07	−.14*	−.36**	.38**	−.33**	.31**	−.18**	−.11^{t}	−.03	1.00			
12	Hispanic	.09	−.03	−.06	−.28**	−.17*	−.27**	−.11	−.04	.02	.00	−.32**	1.00		
13	Pubertal status	−.17*	0.1	0.07	0.07	−0.08	.00	0.03	.00	.28**	.55**	−.04	.02	1.00	
14	Family SES	−.01	−.01	.00	−.39**	.35**	−.35**	.36**	−.30**	−.14*	−.09	.55**	−.18**	−.05	1.00

Note: ^{t} = p < .10, * p < 0.05, ** p < 0.01; SES = socioeconomic status.

Table 3
Generalized Estimating Equations Predicting Inflammation Composite and Monocyte Subtypes.

	Inflammation composite (n = 202)		Classical monocytes (n = 201)		Non-classical monocytes (n = 201)	
Home Neighborhood	b (95 % CI)		b (95 % CI)		b (95 % CI)	
Murder rate	0.04[t]	(-0.00, 0.09)	4.37*	(0.38, 8.35)	−0.65	(-2.04, 0.74)
Exposure to violence (ETV)	−0.03*	(-0.05, 0.00)	−0.41	(-3.12, 2.29)	−0.39	(-1.15, 0.37)
Covariates						
Neighborhood SES	−0.05	(-0.19, 0.07)	5.20	(-4.67, 15.09)	−1.02	(-3.82, 1.78)
Family SES	−0.03	(-0.12, 0.06)	3.92	(-7.71, 15.55)	1.54	(-1.44, 4.52)
Female	−0.19[t]	(-0.41, 0.03)	−22.38*	(-41.04, -3.72)	−2.16	(-7.34, 3.01)
White	0.31*	(0.03, 0.58)	−7.15	(-28.21, 13.89)	−10.65**	(-16.68, -4.61)
Hispanic	0.23*	(0.02, 0.44)	2.31	(-16.78, 21.40)	−6.68[t]	(-13.67, 0.30)
Pubertal status	−0.10	(-0.25, 0.03)	17.07**	(4.53, 29.60)	3.03	(-0.66, 6.73)
Child age	0.02	(-0.19, 0.23)	−6.65	(-22.02, 8.70)	−2.55	(-6.84, 1.74)
	Inflammation composite (n = 197)		Classical monocytes (n = 196)		Non-classical monocytes (n = 196)	
School Neighborhood	b (95 % CI)		b (95 % CI)		b (95 % CI)	
Murder rate	0.00	(-0.02, 0.03)	−0.42	(-4.91, 4.06)	−0.48	(-1.33, 0.37)
Exposure to violence (ETV)	−0.02	(-0.05, 0.00)	−0.57	(-3.34, 2.19)	−0.56	(-1.47, 0.34)
Covariates						
Neighborhood SES	−0.04	(-0.16, 0.07)	2.17	(-5.35, 9.70)	−0.31	(-2.62, 1.99)
Family SES	−0.06	(-0.16, 0.04)	0.11	(-11.93, 12.15)	1.26	(-1.64, 4.17)
Female	−0.20*	(-0.40, -0.00)	−23.91*	(-43.09, -4.73)	−2.19	(-6.98, 2.59)
White	0.26[t]	(-0.02, 0.54)	−15.09	(-34.30, 4.11)	−10.10**	(-15.90, -4.29)
Hispanic	0.18[t]	(-0.00, 0.38)	−8.65	(-26.91, 9.60)	−6.44[t]	(-13.23, 0.34)
Pubertal status	−0.09	(-0.23, 0.05)	16.69**	(5.06, 28.31)	2.98	(-0.88, 6.85)
Child age	0.04	(-0.16, 0.24)	−7.58	(-22.47, 7.30)	−1.96	(-6.10, 2.16)

Note: [t] = $p < .10$, * = $p < 0.05$, **= $p < 0.01$.

Table 4
Supplementary Analyses: Generalized Estimating Equations predicting the Inflammation Composite and Monocyte Subtypes.

	Inflammation composite			Classical monocytes			Non-classical monocytes		
Home neighborhood	b	(95 % CI)	β	b	(95 % CI)	β	b	(95 % CI)	β
Homicides (1 mile)	0.006*	(-0.00, 0.01)	0.19	0.43[t]	(-0.02, 0.89)	0.16	−0.01	(-0.14, 0.12)	−0.01
Exposure to violence	−0.02[t]	(-0.05, 0.00)	−0.09	−0.14	(-3.02, 2.73)	0.00	−0.47	(-1.42, 0.46)	−0.08
Homicides (1/2 mile)	0.01	(-0.00, 0.03)	0.11	0.77	(-0.72, 2.27)	0.10	0.06	(-0.40, 0.54)	0.02
Exposure to violence	−0.02[t]	(-0.05, 0.00)	−0.09	−0.07	(-2.94, 2.78)	0.00	−0.50	(-1.42, 0.40)	−0.08
	Inflammation composite			Classical monocytes			Non-classical monocytes		
School neighborhood	b	(95 % CI)	β	b	(95 % CI)	β	b	(95 % CI)	β
Homicides (1 mile)	0.003	(-0.00, 0.00)	0.12	−0.14	(-0.65, 0.35)	−0.07	−0.06	(-0.15, 0.01)	−0.10
Exposure to violence	−0.02[t]	(-0.05, 0.00)	−0.09	−0.51	(-3.51, 2.47)	−0.02	−0.52	(-1.38, 0.33)	−0.09
Homicides (1/2 mile)	0.01[t]	(-0.00, 0.02)	0.14	−0.64	(-2.07, 0.79)	−0.08	−0.10	(-0.47, 0.26)	−0.04
Exposure to violence	−0.02[t]	(-0.05, 0.00)	−0.09	−0.47	(-3.52, 2.57)	−0.02	−0.58	(-1.38, 0.21)	−0.10

Note: [t] = $p < .10$, * = $p < 0.05$; β = standardized coefficient.

composite and the home neighborhood murder rate ($r = .05$, $p = .42$). Counts of classical monocytes were correlated with the home neighborhood murder rate ($r = .17$, $p = .01$), indicating that youth residing in high-violence neighborhoods evidenced higher counts of classical monocytes, on average. The home neighborhood murder rate was not correlated with counts of non-classical monocytes ($r = .02$, $p = .68$). There was a positive correlation between the home neighborhood murder rate and ETV ($r = .31$, $p < .001$), suggesting that youth residing in high-violence neighborhoods reported more instances of being personally victimized, knowing others who have been victimized, or witnessing community violence in the past year. Murder rates of home and school neighborhoods were moderately correlated ($r = .64$, $p < .001$), suggesting that youth residing in violent neighborhoods tended to also attend schools in violent neighborhoods. The murder rate of school neighborhoods was not correlated with any of the inflammation biomarkers. There were few correlations between the sociodemographic covariates and the inflammation composite and monocyte subtypes. Females evidenced lower scores on the inflammation composite ($r = -.20$, $p = .004$), as did individuals with more advanced puberty ($r = -.17$, $p = .01$). White youth evidenced lower counts of non-classical monocytes than non-White youth, on average ($r = -.14$, $p = .05$).

2.2. Primary analyses

Results of Generalized Estimating Equations predicting the inflammation composite and counts of classical and non-classical monocytes are displayed in Table 3. In each model, unstandardized coefficients and 95 % confidence intervals are presented. In text, unstandardized and standardized (beta) coefficients and p-values are provided for neighborhood-level violence and for self-reported ETV.

2.2.1. Home neighborhood effects

The top panel of Table 3 displays results from the home

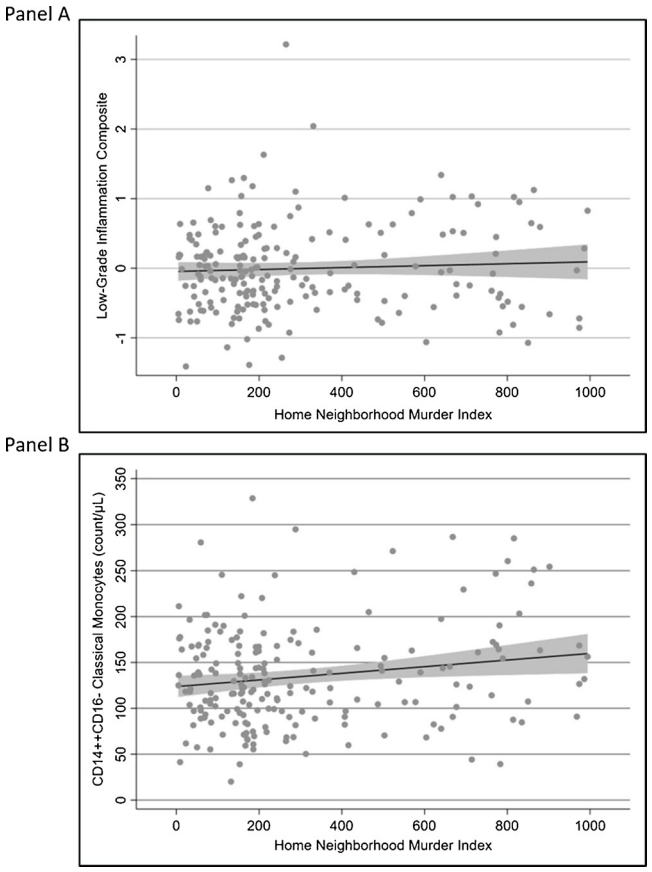

Fig. 1. *Panel A*. Scatterplot depicting the association between the home neighborhood murder rate and scores on the inflammation composite. *Panel B*. Scatterplot depicting the association between the home neighborhood murder rate and counts of CD14+ +CD16 classical monocyte cells. Trend lines and 95 % confidence intervals included.

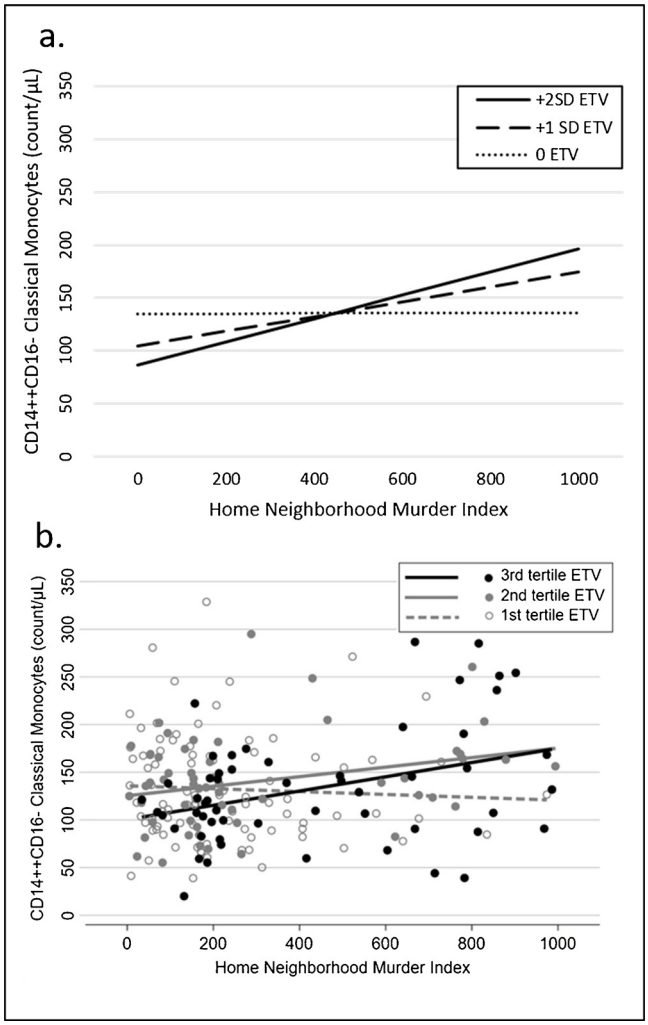

Fig. 2. a: Estimated values of classical monocyte counts at varying levels of home neighborhood-level violence (murder rates) and self-reported exposure to violence (ETV) in covariate-adjusted GEE model. **b**: Scatterplot depicting the association between the home neighborhood murder rate and counts of classical monocytes, separated by tertiles of self-reported ETV.

neighborhood analyses.

2.2.1.1. Inflammation composite. The home neighborhood murder rate was positively associated with the inflammation composite at trend-level significance (b = 0.04, β = 0.18, p = .053) controlling for youths' report of ETV in the past year and the covariates. There was a significant association between ETV and the inflammation composite (b = -0.03, β = -0.14, p = .02). A scatterplot depicting the association between the home neighborhood murder rate and the inflammation composite is displayed in panel A of Fig. 1.

2.2.1.2. Classical monocytes. The home neighborhood murder rate was significantly associated with counts of classical monocytes (b = 4.37, β = 0.20, p = 0.03). A one *SD* increase in the neighborhood murder rate was associated with a 0.20 *SD* increase in the number of classical monocyte cells. A scatterplot depicting the association between the neighborhood murder rate and counts of classical monocytes is shown in panel B of Fig. 1. There was no association between youths' report of ETV and counts of classical monocytes (b = -0.41, β = -0.02, p = .76).

2.2.1.3. Non-classical monocytes. The home neighborhood murder rate was not associated with counts of non-classical monocytes (b = -0.65, β = -0.09, p = .36), nor was ETV (b = -0.39, β = -0.06, p = .31).

2.2.2. School neighborhood effects

The bottom panel of Table 3 displays results from the school neighborhood analyses. In contrast to the effects observed for home neighborhoods, there were no statistically significant associations between the murder rate of school neighborhoods and the inflammation composite (b = 0.003, β = 0.01, p = .83) or monocyte subtypes (classical cells: b = −0.42, β = −0.02, p = .85; non-classical cells: b = −0.48, β = −0.08, p = .27). In these models, there were also no associations between ETV and the inflammation composite (b = −0.02, β = −0.09, p = .14) or monocyte subtypes (classical cells: b = −0.57, β = −0.03, p = .68; non-classical cells: b = −0.56, β = −0.09, p = .22).

2.2.3. Interaction between neighborhood murder rate and youths' exposure to violence

2.2.3.1. Inflammation composite. The neighborhood murder rate and ETV did not interact to predict scores on the inflammation composite, and this was true for both home neighborhoods (b = 0.002, p = 0.64) and school neighborhoods (b = -0.005, p = 0.36).

2.2.3.2. Classical monocytes. Home neighborhood. The home neighborhood murder rate and ETV did interact to predict counts of classical monocytes (b = 1.32, p = 0.003). Fig. 2 panel A depicts the estimated values of classical monocytes at varying levels of home neighborhood-level violence and self-reported ETV. Simple slopes analyses indicated that at high levels of ETV (centered at +1 *SD* and +2 *SD* from mean), the home neighborhood murder rate was positively

associated with counts of classical monocytes (β = .33, p = .002 and β = .52, p < .001, respectively). Among youth with no reported ETV (centered at a value of zero[1]), there was no association between the murder rate and monocytes (β = .00, p = .96).[2] Fig. 2 panel B depicts the scatterplot between home neighborhood-level violence and classical monocytes, separated by tertiles of self-reported ETV. *School neighborhood.* The school neighborhood murder rate and ETV also interacted to predict counts of classical monocytes (b = 0.92, p = 0.006) although, in contrast to the home neighborhood effects, simple slope analyses indicated that both at high levels of ETV (+1 *SD*: β = .07, p = .59; +2 *SD*: β = .23, p = .17) and among those with no reported ETV (β = −.20, p = .14), there was no association between the school neighborhood murder rate and monocytes.[3] Interaction models for both home and school neighborhoods were re-estimated without covariates ($b_{\text{home murder rate X ETV}}$ = 1.22, p = .007; $b_{\text{school murder rate X ETV}}$ = .74, p = .03) and were similar to covariate-adjusted models.

2.2.3.3. Non-classical monocytes. The neighborhood murder rate and ETV did not interact to predict counts of non-classical monocytes, and this was true for both home neighborhoods (b = 0.09, p = 0.48) and school neighborhoods (b = 0.18, p = 0.17).

2.3. Supplementary analyses

Sensitivity analyses were conducted to test whether the associations observed in the primary models were limited to the particular measure of neighborhood violence utilized (i.e. model-based murder rate estimates at the block group level). Models were re-estimated using the sum of homicides within 1 mile and then ½ mile of participants' homes and schools. Because the majority of homicides took place far outside of the block groups in which youths' homes/schools were located, we clustered cases in these sensitivity analyses by Chicago community areas, a larger geographic designation (77 total community areas in Chicago) than block groups. Table 4 displays results from the sensitivity analyses. For each model, we display the unstandardized and standardized coefficients for the main effects of homicides and ETV on the inflammation biomarkers as well as 95 % confidence intervals, although each model also controlled for the same panel of covariates as in the primary models.

2.3.1. Main effects models

2.3.1.1. Inflammation composite. As shown in Table 4, the sum of homicides occurring within 1 mile of participants' homes was positively associated with scores on the inflammation composite (b = 0.006, p = .04), although within ½ mile of home there was no association (b = 0.01, p = .16). There was no association between homicides occurring within 1 mile of schools and the inflammation composite (b = 0.003, p = .19), although within ½ miles the association was trend-level (b = 0.01, p = .09).

2.3.1.2. Classical monocytes. Homicides within 1 mile of homes were associated with classical monocytes at trend-level (b = 0.43, p = .06), although at ½ mile from home there was no association (b = 0.77, p = .31). Homicides occurring within 1 mile (b = -0.14, p = .56) and within ½ mile (b = -0.64, p = .38) of participants' schools were not associated with classical monocytes.

2.3.1.3. Non-classical monocytes. Homicides occurring within 1 mile of homes were not associated with non-classical monocytes (b = -0.01, p = .89) and neither were homicides within ½ mile (b = 0.06, p = .78). Homicides within 1 mile of participants' schools were not associated with non-classical monocytes (b = -0.06, p = .11) and neither were homicides within ½ mile (b = -0.10, p = .57).

2.3.2. Interaction effects models

Consistent with the results observed in the primary analyses, the sum of homicides occurring within 1 mile of participants' homes and their report of ETV interacted to predict classical monocyte counts (b = 0.12, p = 0.003). At a ½ mile radius, this interaction remained significant (b = 0.33, p = 0.001), suggesting this interaction effect was robust to various model specifications. ETV also interacted with the sum of homicides occurring within 1 mile (b = 0.10, p = 0.003) and a ½ mile (b = 0.28, p = 0.008) of participants' schools to predict classical monocyte counts.

3. Discussion

Neighborhood violence is associated with a range of mental and physical health consequences (Shonkoff and Garner, 2012; McLaughlin et al., 2016; Wright et al., 2017), but little is known about the biological processes that confer risk for ill health in these circumstances. At the same time, basic research in disease pathogenesis and applied work in health psychology have identified low-grade inflammation as a biological process that, beginning in the first decades of life, is both induced by chronic stress and a driver of cardiometabolic diseases that present at various stages throughout the lifecourse (Miller et al., 2011). Findings from the current study contribute to this literature by demonstrating that in urban youth, neighborhood violence is associated with biomarkers of inflammatory activity. Specifically, we observed that adolescents residing in high-violence neighborhoods evidenced higher numbers of classical (CD14++CD16-) monocyte cells relative to their peers residing in less violent neighborhoods. Neighborhood violence was not consistently associated with traditional biomarkers of inflammation, as reflected in a composite of CRP, interleukin-6, interleukin-8, interleukin-10 and TNF-α. In general, the findings were specific to violence occurring in the neighborhoods where youth lived as opposed to the neighborhoods where they attended school.

We also observed a statistical interaction, whereby neighborhood-level violence related to classical monocyte counts among youth who reported having been exposed to violence in the previous year. Given work suggesting that witnessing or being a victim of violence can increase feelings of fear, stress- or trauma-related symptoms, and that it reduces feelings of safety and security in one's environment (see

[1] As would be expected, the distribution of frequency scores on the Exposure to Violence (ETV) measure was zero-inflated and positively skewed, thus 1 *SD* below the mean on ETV was outside of the range of values. Therefore, we estimated the simple slope of the murder rate on classical monocytes for those with an ETV frequency score of 0 (i.e. no direct exposure to community violence).

[2] Additional simple slopes estimates indicated that among those residing in low-violence neighborhoods (-1 *SD*), there was a negative association between ETV and monocytes (β = -.29, p = .001) and in high-violence neighborhoods (+2 *SDs*), there was a positive association between ETV and monocytes (β = .28, p = .05). It is difficult to interpret the negative association between ETV and monocytes among those in low-violence neighborhoods with confidence. This is because there are very few cases residing in low-violence neighborhoods who report high ETV (e.g. among those in neighborhoods in the lowest tertile of violence, only n = 6 reported ETV scores in the highest tertile of ETV). Because the distribution of ETV scores is so positively skewed among those in the lowest-violence neighborhoods, we suspect that the negative association may be a statistical artifact primarily driven by the few cases reporting high ETV having large influence on the regression line.

[3] Additional simple slopes estimates indicated that the statistical interaction between ETV and school neighborhood murder rates was driven by a negative association between ETV and classical monocytes among those attending school in low-violence neighborhoods (-1 *SD*; β = -.21, p = .01) and a positive association between ETV and monocytes among those in high-violence neighborhoods (+2 *SDs*; β = .24, p = .05). Consistent with the observation and argument made in Footnote 2, we suspect that the negative association between ETV and classical monocytes among those attending school in low-violence neighborhoods may be a statistical artifact.

Margolin and Gordis, 2004; Foster and Brooks-Gunn, 2009), one possible interpretation of this finding is that violent incidents, and the community's response to violence, may simply be more salient or perceived as more threatening for individuals with ETV experience—resulting in higher pro-inflammatory activity. Another possibility, consistent with the idea that ETV can have wide-ranging developmental effects (e.g. that it can diminish behavioral, cognitive and self-regulatory capacities, and disrupt social connections/support; Margolin and Gordis, 2004; Foster and Brooks-Gunn, 2009), is that ETV undermines coping strategies (Foster and Brooks-Gunn, 2009), which may make violence-exposed youth more vulnerable to neighborhood-level factors. One consideration regarding the interaction we observed, however, is that there were few individuals in our sample living in high-violence neighborhoods who simultaneously reported *low levels* of violence exposure (consistent with what is known about the increased risk for victimization in high-violence neighborhoods; Sampson and Lauritsen, 1990), a condition which would be preferable from an analytic/inferential perspective.

Our findings regarding classical monocytes converge with experimental studies of rodents, which show that under conditions of chronic social defeat, classical monocytes are mobilized into circulation from the bone marrow via sympathetic innervation (Weber et al., 2017). These cells exhibit a strong pro-inflammatory skew, marked by exaggerated cytokine responses to microbes and relative insensitivity to inhibition by glucocorticoids. After chronic social defeat they also migrate to the brain, where they augment inflammatory signaling in the amygdala, prefrontal cortex, and hippocampus, and thereby contribute to anxiety-like behavior (Weber et al., 2017, 2019; Niraula et al., 2018, 2019). Consistent with this neuro-immune signaling observed in rodents, recent neuroimaging studies in humans also have shown associations between functional connectivity of these brain regions and the extent of peripheral inflammatory activity (Muscatell et al., 2015; Felger et al., 2016; Nusslock et al., 2019), including the prevalence of classical monocytes (Nusslock et al., 2019). The clinical implications of these violence-brain-immune connections have yet to be defined. However, a recent study of adults (Tawakol et al., 2019) using whole-body PET/CT imaging suggests that increased amygdala activity, hematopoietic activity in bone marrow, and arterial inflammation may contribute to heightened risk for cardiovascular events among those residing in high crime and low socioeconomic status neighborhoods. Additional research will be needed to determine what, if any, cardiovascular implications the violence-inflammation association observed here has for youth.

In contrast to the associations observed for home neighborhoods, we found little evidence that violence around schools was associated with inflammation. This is notable given the moderate correlation between the murder rates of home and school neighborhoods ($r = 0.64$). Homicides tend to occur during the night hours (e.g., Pizarro, 2008), times when youth are likely to be in their home neighborhoods as opposed to their school neighborhoods. Thus, one potential explanation for the lack of school neighborhood effects is that homicides occurring around the home may be more salient as youth are more likely to be in closer proximity to homicides as they occur when they are in their home neighborhood as opposed to when they are in their school neighborhood.

A strength of the current study is that we conducted a set of sensitivity analyses to test the robustness of findings. The most robust findings were for the interaction between home neighborhood murder rates and personal violence exposure. Across multiple different specifications, this interaction was associated with classical monocyte counts. The interaction between the school neighborhood murder rate and youths' report of exposure to violence was also significant in sensitivity analyses. However, data visualization and simple slopes analyses indicated that, in contrast to home neighborhood effects, the association between school neighborhood-level violence and classical monocytes was not conditional on youths' report of exposure to violence. Instead, the interaction was primarily driven by a small negative correlation between ETV and classical monocytes among youth attending school in low-violence neighborhoods, consistent in direction to effects in home neighborhoods.

Relative to the interactions, the main effects relating neighborhood-level violence to inflammatory outcomes were more sensitive to model specifications. This variability was particularly evident across unadjusted and adjusted models predicting the inflammatory biomarker composite. The strength of the association between neighborhood-level violence and classical monocytes also varied across model specifications, but not as markedly. There was also little evidence that self-reported ETV was associated with the inflammatory biomarkers. Although one model (i.e. an adjusted model predicting the inflammation composite from ETV and home neighborhood murder), did indicate evidence of a negative association between ETV and inflammation, this was the only condition of many in which ETV was a statistically significant predictor. Collectively, the findings suggest that neither the main effect of ETV nor the main effect of neighborhood-level violence were robustly associated with the inflammatory composite. The main effects results predicting classical monocytes, in contrast, initially suggested that neighborhood murder was a stronger predictor than self-reported ETV. However, the interaction that was later observed between the two variables suggested that it was the interaction between settings-level factors and individual-level experience that best predicted classical monocytes.

It is not immediately apparent why the inflammatory biomarker composite was so inconsistently associated with neighborhood violence and ETV. These results stand in contrast to prior studies reporting positive associations between neighborhood crime and CRP concentration (Browning et al., 2012; Broyles et al., 2012). One possibility is that because youth in our sample were healthy (and therefore their levels of cytokines and CRP were near the lower limits of the assay's range of detection), our estimates of cytokine and CRP levels may simply be less precise than our measure of low-grade inflammation based on counts of circulating monocytes, which relies on a flow cytometry protocol that is not affected by the same methodological/detection challenges as immunoassay.

The current study is not without several limitations. First, given the study's design, we are unable to establish a causal link between neighborhood violence and inflammatory activity. Although we included several individual- and settings-level covariates in our analyses, because of the correlational study design, we cannot rule out the possibility of selection bias and additionally that unobserved variable(s) may be biasing model estimates. For example, it may be that other relevant neighborhood factors (e.g., low walkability, toxins/pollutants, and noise) or individual factors (e.g., perceptions of safety and collective efficacy) that covary with neighborhood- and individual-level violence exposure also covary with individual levels of low-grade inflammation. For this reason, future studies that utilize design features and statistical methods that can enhance causal inference will be necessary. With this in mind, experimental evidence indicates that neighborhood settings can, in principle, have causal effects on cardiometabolic health outcomes. Indeed, one large-scale experimental study (Ludwig et al., 2011) showed that moving from high-poverty to low-poverty neighborhoods resulted in reductions in extreme obesity and diabetes among adults. Future research would benefit from additional experimental studies of this nature. But, given the expense of these types of studies, an interim step towards clarifying the associations observed here and for enhancing causal inference would be to ask similar questions longitudinally. For example, having multiple measurement occasions would allow one to test whether violence predicts change in pro-inflammatory biomarkers over time—reducing but not eliminating the problem of ambiguous temporal precedence that accompanies cross-sectional analyses. Other methods that leverage panel data to enhance causal inference include fixed-effects models (see Foster, 2010), which could be used to estimate quasi-causal within-

person effects of violence on inflammatory outcomes, holding constant many unobserved yet confounding between-person factors. Such designs have demonstrated effects of residential proximity to homicides on cognitive functioning of youth (e.g. Sharkey et al., 2012).

Another consideration has to do with our sample size, which we acknowledge may be considered modest compared to some previous epidemiological studies measuring CRP and cytokine markers of inflammation. Having said this, we believe that our more mechanistic approach to testing links between experiential stress and pro-inflammatory processes (e.g., utilizing flow cytometry to enumerate specific subpopulations of monocyte cells) is a central strength of the sample and study and offsets some sample size related concern. An additional consideration is that because of the eligibility criteria we established for who could participate in the study, the results we report in this analysis may not be generalizable to populations of youth who were excluded (e.g. those with chronic medical or psychiatric illnesses). Another limitation has to do with the way in which neighborhoods were measured. Although our use of multiple measures of neighborhood boundaries (i.e. U.S. Census block groups, 1-mile, and ½-mile radial buffers around youths' homes and schools) strengthens the inferences we can draw from this study, we acknowledge the possibility that these measures may differ from what individuals actually consider to be their neighborhoods. Recent work has begun to utilize alternative geospatial methods, primarily using GPS technologies, to measure where individuals actually travel on a daily basis in order to generate more valid measurements of individual "neighborhoods", which often do not align with Census-derived boundaries (Browning and Soller, 2014). However, these new approaches are not without their own methodological and ethical challenges (Roy, 2017).

3.1. Conclusions

The current study documents the first evidence in adolescents of an association between neighborhood violence and counts of classical monocyte cells, suggesting that contextual stressors such as violence can mobilize this specific pro-inflammatory leukocyte subset into circulation—a plausible biological mechanism which may contribute to disease pathogenesis among youth residing in high-violence contexts. In particular, we found evidence that home neighborhood-level violence and counts of classical monocytes were associated with one another only among youth who reported having been exposed to violence in the previous year, suggesting a subpopulation who may be most vulnerable to the physical health consequences of community violence. In contrast to previous work, we observed less robust evidence that violence was associated with cytokine markers of low-grade inflammation. Future research concerning the ways in which contextual stressors shape cellular components of the inflammatory process specifically may be especially productive in terms of generating a better mechanistic understanding of this stress process and ultimately designing and assessing intervention efforts to reduce the negative health effects of community violence on youth.

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Declaration of Competing Interest

None.

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